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(54) Title: COMPOSITIONS AND METHODS FOR ENHANCED ABSORPTION OF HYDROPHILIC THERAPEUTIC AGENTS

(57) Abstract: The present invention relates to pharmaceutical compositions, pharmaceutical systems, and methods for enhanced absorption of hydrophilic therapeutic agents. Compositions and systems of the present invention include an absorption enhancing carrier, where the carrier is formed from a combination of at least two surfactants, at least one of which is hydrophilic. A hydrophilic therapeutic agent can be incorporated into the composition, or can be co-administered with the composition as part of a pharmaceutical system. The invention also provides methods of treatment with hydrophilic therapeutic agents using these compositions and systems.

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1  
COMPOSITIONS AND METHODS FOR  
ENHANCED ABSORPTION OF HYDROPHILIC  
THERAPEUTIC AGENTS

5  
FIELD OF THE INVENTION

The present invention relates to drug, nutrient and diagnostic agent delivery systems, and in particular to pharmaceutical systems and methods for the improved delivery and enhanced absorption of hydrophilic therapeutic agents.

BACKGROUND

10 Hydrophilic therapeutic agents present difficult problems in formulation. While these therapeutic agents are readily soluble in water, and are easily dissolved in the gastrointestinal environment, simple dissolution is not sufficient to provide efficient bioabsorption of the therapeutic agent. Barriers to absorption are presented by the mucous layer, the intestinal epithelial cell membrane, and the junctional structure such as tight  
15 junctions between the epithelial cells. Due to the presence of the negatively charged mucosal layer, significant electrostatic binding or repulsion of charged molecules can be encountered. The epithelial cell membranes are composed of phospholipid bilayers in which proteins are embedded via the hydrophobic segments. These bilayers at the apical and/or basolateral cell surface represent very strong barriers for transport of hydrophilic  
20 substances, including peptides and proteins. Frequently, hydrophilic therapeutic agents are also subject to enzymatic attack and are degraded before they can be presented to the absorption site.

Some hydrophilic drugs such as acyclovir, foscarnet, tiludronate, pamidronate, alendronate, acarbose, cromolyn sodium, aminoglycoside and cephalosporin antibiotics  
25 are poorly absorbed from the gastro-intestinal tract, due to their low octanol-water partition coefficient, charge, and/or size.

Large water-soluble polymers, such as peptides, proteins, genetic material, vaccines and oligonucleotides, are not well absorbed from the intestine, primarily due to their low membrane permeability and enzymatic inactivation. The mammalian body  
30 possesses several efficient mechanisms to restrict the entry of macromolecules. These mechanisms include the presence of significant levels of enzymatic activity at various locations prior to entry into systemic circulation.

1        Thus, numerous barriers to absorption of hydrophilic therapeutic agents are present, and these barriers inhibit the effective absorption both of small hydrophilic therapeutic agents, such as conventional non-peptidic drugs, and of macromolecular hydrophilic therapeutic agents, such as proteins, peptides, vaccines and the like.

5        Much effort has been expended to develop methods of overcoming these absorption barriers. For example, the enzymatic barrier can be attacked by administering enzyme inhibitors to prevent or at least lessen the extent of presystemic degradation in the gastrointestinal tract (*see, e.g.,* Bernkop-Schnurch, "The use of inhibitory agents to overcome the enzymatic barrier to perorally administered therapeutic peptides and proteins", *Journal of Controlled Release*, 52, 1-16 (1998)). Other efforts have focused on, for example, the use of absorption promoters to enhance epithelial permeability (*e.g.,* LeCluyse and Sutton, "In vitro models for selection of development candidates. Permeability studies to define mechanisms of absorption enhancement", *Advanced Drug Delivery Reviews*, 23, 163-183 (1997)). However, the effectiveness of absorption  
10        enhancers such as permeability enhancers or enzyme inhibitors depends upon the ability of a pharmaceutical carrier to effectively present the absorption enhancers and the hydrophilic therapeutic agent to the absorption site, and prior efforts have not provided carriers which can do so efficiently. Moreover, maintaining effective carrier concentrations at the epithelium is not easily controlled in vivo. Too little carrier, or  
15        carrier concentrations only briefly maintained, may be ineffective. Too much carrier, or carrier concentrations maintained for too long, may result in compromised safety.

      Frequently, carrier compositions for hydrophilic therapeutic agents include or are based on triglycerides. For example, U.S. Patent Nos. 5,444,041, 5,646,109 and 5,633,226 to Owen et al. are directed to water-in-oil ("w/o") microemulsions for delivering water-  
25        soluble biological actives, such as proteins or peptides. The water-in-oil microemulsions convert into oil-in-water ("o/w") emulsions upon ingestion. The active agent is initially stored in the internal water phase of the w/o microemulsion, and is released when the composition converts to an o/w emulsion upon mixing with bodily fluids. Other oil-based or oil-containing formulations are taught in, for example, U.S. Patent No. 5,120,710 to  
30        Liedtke, U.S. Patent No. 5,656,289 to Cho et al. These triglyceride-containing formulations, however, suffer from several disadvantages.

1 U.S. Patent No. 5,206,219 to Desai, for example, teaches compositions having a  
particle size of 5 to 50 microns. Typically, emulsions formed from triglyceride-containing  
compositions contain colloidal oil particles which are relatively large, ranging from  
several hundred nanometers to several microns in diameter, in a broad particle size  
5 distribution. Since the particle sizes are on the order of or greater than the wavelength  
range of visible light, such emulsions, when prepared in an emulsion dosage form, are  
visibly "cloudy" or "milky" to the naked eye. Emulsions are thermodynamically unstable,  
and colloidal emulsion particles will spontaneously agglomerate, eventually leading to  
complete phase separation. The tendency to agglomerate and phase separate presents  
10 problems of storage and handling, and increases the likelihood that pharmaceutical  
emulsions initially properly prepared will be in a less optimal, less effective, and poorly-  
characterized state upon ultimate administration to a patient. Uncharacterized degradation  
is particularly disadvantageous, since increased particle size slows the rate of transport of  
the colloidal particle and digestion of the oil component, and hence the rate and extent of  
15 absorption of the therapeutic agent. These problems lead to poorly-characterized and  
potentially harmful changes in the effective dosage received by the patient, and/or the rate  
of drug uptake. Moreover, changes in colloidal emulsion particle size are also believed to  
render absorption more sensitive to and dependent upon conditions in the gastrointestinal  
tract, such as pH, enzyme activity, bile components, and stomach contents. Such  
20 uncertainty in the rate and extent of ultimate absorption of the therapeutic agent severely  
compromises the medical professional's ability to safely administer therapeutically  
effective dosages. In addition, when such compositions are administered parenterally, the  
presence of large particles can block blood capillaries, further compromising patient  
safety.

25 U.S. Patent No. 5,626,869 to Nyqvist et al. discloses compositions that would  
likely produce discrete lipid particles of relatively large size *in vivo*. Such particles suffer  
from the disadvantages of large size and low diffusivity, and are unable to effectively  
present any absorption enhancing components to the site of absorption.

30 A further disadvantage of conventional triglyceride-containing compositions is the  
dependence of therapeutic agent absorption on the rate and extent of lipolysis. Ultimately  
the triglyceride must be digested and the therapeutic agent must be released in order to be  
absorbed through the intestinal mucosa. The triglyceride carrier is emulsified by bile salts



1 and hydrolyzed, primarily by pancreatic lipase. The rate and extent of lipolysis, however,  
are dependent upon several factors that are difficult to adequately control. For example,  
the amount and rate of bile salt secretion affect the lipolysis of the triglycerides, and the  
bile salt secretion can vary with stomach contents, with metabolic abnormalities, and with  
5 functional changes of the liver, bile ducts, gall bladder and intestine. Lipase availability in  
patients with decreased pancreatic secretory function, such as cystic fibrosis or chronic  
pancreatitis, may be undesirably low, resulting in a slow and incomplete triglyceride  
lipolysis. The activity of lipase is pH dependent, with deactivation occurring at about pH  
3, so that the lipolysis rate will vary with stomach contents, and may be insufficient in  
10 patients with gastric acid hyper-secretion. Moreover, certain surfactants commonly used  
in the preparation of pharmaceutical emulsions, such as polyethoxylated castor oils, may  
themselves act as inhibitors of lipolysis.

Other carrier formulations avoid the use of triglycerides, but still suffer  
disadvantages. For example, U.S. Patent No. 5,653,987 to Modi et al. is directed to  
15 pharmaceutical formulations for oral or nasal delivery of proteinaceous pharmaceutical  
agents using small amounts of particular surfactants and a protease inhibitor in an aqueous  
medium as absorption enhancers. However, in the gastrointestinal tract, where the volume  
of liquids is large and motility is great, polar drugs and the protease inhibitor are diluted  
even further upon administration, thus negating any potential benefits, since the  
20 composition is unable to deliver meaningful amounts of the absorption enhancers and  
pharmaceutical agents to the absorption site.

Thus, there is a need for pharmaceutical compositions that overcome the  
limitations of conventional formulations, to provide effective delivery of absorption  
enhancers and enhanced absorption of hydrophilic therapeutic agents.

## 25 SUMMARY OF THE INVENTION

The present invention provides triglyceride-free pharmaceutical systems for  
enhanced bioabsorption of hydrophilic therapeutic agents. It has been surprisingly found  
that pharmaceutical compositions having absorption enhancing properties can be provided  
by using a combination of surfactants in amounts such that when the pharmaceutical  
30 composition is mixed with an aqueous diluent, an aqueous dispersion having a very small  
average particle size is formed. Such compositions can be co-administered with a  
hydrophilic therapeutic agent to increase the rate and/or extent of bioabsorption of the

1 hydrophilic therapeutic agent, or can be provided with a hydrophilic therapeutic agent in the preconcentrate composition or in a diluent solution.

5 In one embodiment, the present invention relates to triglyceride-free pharmaceutical systems having a dosage form of an absorption enhancing composition comprising at least two surfactants, at least one of which is hydrophilic, and a hydrophilic therapeutic agent. The surfactants are present in amounts such that the carrier forms an aqueous dispersion having a very small average particle size upon mixing with an aqueous diluent. The hydrophilic therapeutic agent can be solubilized, suspended, or partially solubilized and suspended, in the absorption enhancing carrier. Alternatively, the 10 hydrophilic therapeutic agent can be provided separately, for co-administration with the dosage form of the absorption enhancing composition.

In another embodiment, the present invention provides a triglyceride-free pharmaceutical system for enhanced absorption of a hydrophilic therapeutic agent, including a dosage form of an absorption enhancing composition, and a hydrophilic 15 therapeutic agent, wherein the absorption enhancing composition has at least one hydrophilic surfactant and at least one hydrophobic surfactant. The surfactants are present in amounts such that the carrier forms an aqueous dispersion having a very small average particle size upon mixing with an aqueous diluent. The hydrophilic therapeutic agent can be solubilized, suspended, or partially solubilized and suspended, in the dosage form of 20 the absorption enhancing composition, or provided in a separate dosage form.

In another embodiment, the present invention provides a method of improving the bioabsorption of a hydrophilic therapeutic agent administered to a patient. The method includes the steps of providing a dosage form of an absorption enhancing composition, providing a hydrophilic therapeutic agent, and administering the dosage form of the 25 absorption enhancing composition and the hydrophilic therapeutic agent to a patient. The method improves bioabsorption by improving the consistency of delivery of the hydrophilic therapeutic agent to the absorption site, and providing absorption enhancers at the absorption site.

30 These and other features of the present invention will become more fully apparent from the following description and appended claims, or may be learned by the practice of the invention as set forth hereinafter.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention overcomes the problems described above characteristic of conventional formulations of hydrophilic therapeutic agents by providing unique pharmaceutical systems for enhanced absorption of hydrophilic therapeutic agents. The pharmaceutical systems include absorption-enhancing components which, when the compositions are mixed with an aqueous diluent either *in vitro* or *in vivo*, form aqueous dispersions having a very small particle size. The combination of absorption enhancing compounds at relatively high concentration, very small particle sizes upon dispersion, and the absence of triglycerides unexpectedly enhances the rate, extent and/or consistency of bioabsorption of hydrophilic therapeutic agents present in, or co-administered with, the absorption enhancing compositions.

The term "absorption enhancement" as used herein means an improvement in one or more of the rate of bioabsorption, the extent of bioabsorption, and the consistency of the rate and/or extent of bioabsorption. Without wishing to be bound by theory, it is believed that the absorption enhancement provided by the pharmaceutical systems of the present invention is a result of one or more of the following factors:

- (1) effective presentation of an absorption enhancer to the site of enhancement;
- (2) modulation of facilitated/active transport;
- (3) transcellular permeability enhancement through favorable membrane perturbations;
- (4) inhibition of efflux related transporters;
- (5) inhibition of luminal or cellular enzymatic inactivation;
- (6) paracellular transport enhancement through loosening of tight junctions;
- (7) induction of specific transporters to facilitate transport;
- (8) altered biological binding characteristics;
- (9) reduced degradation of the hydrophilic therapeutic agent;
- (10) induction of transient water channels; and/or
- (11) increased partitioning of the hydrophilic therapeutic agent by association with the absorption enhancer.

1           A.     Pharmaceutical Compositions and Methods

          In one embodiment, the present invention provides a triglyceride-free pharmaceutical system including an absorption enhancing composition. The absorption enhancing composition includes at least two surfactants, at least one of which is a hydrophilic surfactant. Preferably, the carrier includes at least one hydrophilic surfactant and at least one hydrophobic surfactant. The surfactants are present in amounts such that upon dilution with an aqueous diluent, either *in vitro* or *in vivo*, the carrier forms an aqueous dispersion having a small average particle size. The hydrophilic and hydrophobic surfactants are believed to function as absorption enhancers, and the hydrophilic surfactant additionally assists the functionality of other absorption enhancing hydrophilic or hydrophobic surfactants.

          1.     Surfactants

          The absorption enhancing composition includes at least two surfactants, at least one of which is a hydrophilic surfactant. Preferably, the composition includes at least one hydrophilic surfactant and at least one hydrophobic surfactant. As is well known in the art, the terms "hydrophilic" and "hydrophobic" are relative terms. To function as a surfactant, a compound must necessarily include polar or charged hydrophilic moieties as well as non-polar hydrophobic (lipophilic) moieties; *i.e.*, a surfactant compound must be amphiphilic. An empirical parameter commonly used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance ("HLB" value). Surfactants with lower HLB values are more hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions.

          Using HLB values as a rough guide, hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, hydrophobic surfactants are compounds having an HLB value less than about 10.

          It should be appreciated that the HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions. For many important surfactants, including several polyethoxylated surfactants, it has been reported that HLB values can differ by as much as about 8 HLB units,

1 depending upon the empirical method chosen to determine the HLB value (Schott, *J. Pharm. Sciences*, 79(1), 87-88 (1990)). Likewise, for certain polypropylene oxide  
containing block copolymers (PLURONIC® surfactants, BASF Corp.), the HLB values  
may not accurately reflect the true physical chemical nature of the compounds. Finally,  
5 commercial surfactant products are generally not pure compounds, but are complex  
mixtures of compounds, and the HLB value reported for a particular compound may more  
accurately be characteristic of the commercial product of which the compound is a major  
component. Different commercial products having the same primary surfactant  
component can, and typically do, have different HLB values. In addition, a certain  
10 amount of lot-to-lot variability is expected even for a single commercial surfactant  
product. Keeping these inherent difficulties in mind, and using HLB values as a guide,  
one skilled in the art can readily identify surfactants having suitable hydrophilicity or  
hydrophobicity for use in the present invention, as described herein.

15 The hydrophilic surfactant can be any hydrophilic surfactant suitable for use in  
pharmaceutical compositions. Such surfactants can be anionic, cationic, zwitterionic or  
non-ionic, although non-ionic hydrophilic surfactants are presently preferred. As  
discussed above, these non-ionic hydrophilic surfactants will generally have HLB values  
greater than about 10. Mixtures of hydrophilic surfactants are also within the scope of the  
invention.

20 Similarly, the hydrophobic surfactant can be any hydrophobic surfactant suitable  
for use in pharmaceutical compositions. In general, suitable hydrophobic surfactants will  
have an HLB value less than about 10. Mixtures of hydrophobic surfactants are also  
within the scope of the invention.

25 The choice of specific hydrophobic and hydrophilic surfactants should be made  
keeping in mind the particular hydrophilic therapeutic agent to be used in the composition,  
and the range of polarity appropriate for the chosen hydrophilic therapeutic agent, as  
discussed in more detail below. With these general principles in mind, a very broad range  
of surfactants is suitable for use in the present invention. Such surfactants can be grouped  
into the following general chemical classes detailed in the Tables herein. The HLB values  
30 given in the Tables below generally represent the HLB value as reported by the  
manufacturer of the corresponding commercial product. In cases where more than one  
commercial product is listed, the HLB value in the Tables is the value as reported for one



of the commercial products, a rough average of the reported values, or a value that, in the judgment of the present inventors, is more reliable. It should be emphasized that the invention is not limited to the surfactants in the Tables, which show representative, but not exclusive, lists of available surfactants.

#### 1.1. Polyethoxylated Fatty Acids

Although polyethylene glycol (PEG) itself does not function as a surfactant, a variety of PEG-fatty acid esters have useful surfactant properties. Among the PEG-fatty acid monoesters, esters of lauric acid, oleic acid, and stearic acid are especially useful. Among the surfactants of Table 1, preferred hydrophilic surfactants include PEG-8 laurate, PEG-8 oleate, PEG-8 stearate, PEG-9 oleate, PEG-10 laurate, PEG-10 oleate, PEG-12 laurate, PEG-12 oleate, PEG-15 oleate, PEG-20 laurate and PEG-20 oleate. Examples of polyethoxylated fatty acid monoester surfactants commercially available are shown in Table 1.

Table 1: PEG-Fatty Acid Monoester Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG 4-100 monolaurate	Crodet L series (Croda)	>9
PEG 4-100 monooleate	Crodet O series (Croda)	>8
PEG 4-100 monostearate	Crodet S series (Croda), Myrj Series (Atlas/ICI)	>6
PEG 400 distearate	Cithrol 4DS series (Croda)	>10
PEG 100,200,300 monolaurate	Cithrol ML series (Croda)	>10
PEG 100,200,300 monooleate	Cithrol MO series (Croda)	>10
PEG 400 dioleate	Cithrol 4DO series (Croda)	>10
PEG 400-1000 monostearate	Cithrol MS series (Croda)	>10
PEG-1 stearate	Nikkol MYS-1EX (Nikko), Coster K1 (Condea)	2
PEG-2 stearate	Nikkol MYS-2 (Nikko)	4
PEG-2 oleate	Nikkol MYO-2 (Nikko)	4.5
PEG-4 laurate	Mapeg® 200 ML (PPG), Kessco® PEG 200ML (Stepan), LIPOPEG 2L (LIPO Chem.)	9.3
PEG-4 oleate	Mapeg® 200 MO (PPG), Kessco® PEG200 MO (Stepan),	8.3
PEG-4 stearate	Kessco® PEG 200 MS (Stepan), Hodag 20 S (Calgene), Nikkol MYS-4 (Nikko)	6.5

## 10

1	PEG-5 stearate	Nikkol TMGS-5 (Nikko)	9.5
	PEG-5 oleate	Nikkol TMGO-5 (Nikko)	9.5
	PEG-6 oleate	Algon OL 60 (Auschem SpA), Kessco® PEG 300 MO (Stepan), Nikkol MYO-6 (Nikko), Emulgante A6 (Condea)	8.5
5	PEG-7 oleate	Algon OL 70 (Auschem SpA)	10.4
	PEG-6 laurate	Kessco® PEG300 ML (Stepan)	11.4
	PEG-7 laurate	Lauridac 7 (Condea)	13
	PEG-6 stearate	Kessco® PEG300 MS (Stepan)	9.7
	PEG-8 laurate	Mapeg® 400 ML (PPG), LIPOPEG 4DL(Lipo Chem.)	13
10	PEG-8 oleate	Mapeg® 400 MO (PPG), Emulgante A8 (Condea); Kessco PEG 400 MO (Stepan)	12
	PEG-8 stearate	Mapeg® 400 MS (PPG), Myrj 45	12
	PEG-9 oleate	Emulgante A9 (Condea)	>10
	PEG-9 stearate	Cremophor S9 (BASF)	>10
15	PEG-10 laurate	Nikkol MYL-10 (Nikko), Lauridac 10 (Croda)	13
	PEG-10 oleate	Nikkol MYO-10 (Nikko)	11
	PEG-10 stearate	Nikkol MYS-10 (Nikko), Coster K100 (Condea)	11
	PEG-12 laurate	Kessco® PEG 600ML (Stepan)	15
	PEG-12 oleate	Kessco® PEG 600MO (Stepan)	14
20	PEG-12 ricinoleate	(CAS # 9004-97-1)	>10
	PEG-12 stearate	Mapeg® 600 MS (PPG), Kessco® PEG 600MS (Stepan)	14
	PEG-15 stearate	Nikkol TMGS-15 (Nikko), Koster K15 (Condea)	14
	PEG-15 oleate	Nikkol TMGO-15 (Nikko)	15
	PEG-20 laurate	Kessco® PEG 1000 ML (Stepan)	17
25	PEG-20 oleate	Kessco® PEG 1000 MO (Stepan)	15
	PEG-20 stearate	Mapeg® 1000 MS (PPG), Kessco® PEG 1000 MS (Stepan), Myrj 49	16
	PEG-25 stearate	Nikkol MYS-25 (Nikko)	15
	PEG-32 laurate	Kessco® PEG 1540 ML (Stepan)	16
30	PEG-32 oleate	Kessco® PEG 1540 MO (Stepan)	17
	PEG-32 stearate	Kessco® PEG 1540 MS (Stepan)	17
	PEG-30 stearate	Myrj 51	>10

1	PEG-40 laurate	Crodet L40 (Croda)	17.9
	PEG-40 oleate	Crodet O40 (Croda)	17.4
	PEG-40 stearate	Myrj 52, Emerest® 2715 (Henkel), Nikkol MYS-40 (Nikko)	>10
5	PEG-45 stearate	Nikkol MYS-45 (Nikko)	18
	PEG-50 stearate	Myrj 53	>10
	PEG-55 stearate	Nikkol MYS-55 (Nikko)	18
	PEG-100 oleate	Crodet O-100 (Croda)	18.8
	PEG-100 stearate	Myrj 59, Arlacel 165 (ICI)	19
10	PEG-200 oleate	Albunol 200 MO (Taiwan Surf.)	>10
	PEG-400 oleate	LACTOMUL (Henkel), Albunol 400 MO (Taiwan Surf.)	>10
	PEG-600 oleate	Albunol 600 MO (Taiwan Surf.)	>10

## 1.2 PEG-Fatty Acid Diesters

15 Polyethylene glycol (PEG) fatty acid diesters are also suitable for use as surfactants in the compositions of the present invention. Among the surfactants in Table 2, preferred hydrophilic surfactants include PEG-20 dilaurate, PEG-20 dioleate, PEG-20 distearate, PEG-32 dilaurate and PEG-32 dioleate. Representative PEG-fatty acid diesters are shown in Table 2.

20 Table 2: PEG-Fatty Acid Diester Surfactants

	COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
	PEG-4 dilaurate	Mapeg® 200 DL (PPG), Kessco® PEG 200 DL (Stepan), LIPOPEG 2-DL (Lipo Chem.)	7
25	PEG-4 dioleate	Mapeg® 200 DO (PPG),	6
	PEG-4 distearate	Kessco® 200 DS (Stepan)	5
	PEG-6 dilaurate	Kessco® PEG 300 DL (Stepan)	9.8
	PEG-6 dioleate	Kessco® PEG 300 DO (Stepan)	7.2
	PEG-6 distearate	Kessco® PEG 300 DS (Stepan)	6.5
30	PEG-8 dilaurate	Mapeg® 400 DL (PPG), Kessco® PEG 400 DL (Stepan), LIPOPEG 4 DL (Lipo Chem.)	11
	PEG-8 dioleate	Mapeg® 400 DO (PPG), Kessco® PEG 400 DO (Stepan), LIPOPEG 4 DO (Lipo Chem.)	8.8

1	PEG-8 distearate	Mapeg® 400 DS (PPG), CDS 400 (Nikkol)	11
	PEG-10 dipalmitate	Polyaldo 2PKFG	>10
	PEG-12 dilaurate	Kessco® PEG 600 DL (Stepan)	11.7
	PEG-12 distearate	Kessco® PEG 600 DS (Stepan)	10.7
5	PEG-12 dioleate	Mapeg® 600 DO (PPG), Kessco® 600 DO (Stepan)	10
	PEG-20 dilaurate	Kessco® PEG 1000 DL (Stepan)	15
	PEG-20 dioleate	Kessco® PEG 1000 DO (Stepan)	13
	PEG-20 distearate	Kessco® PEG 1000 DS (Stepan)	12
10	PEG-32 dilaurate	Kessco® PEG 1540 DL (Stepan)	16
	PEG-32 dioleate	Kessco® PEG 1540 DO (Stepan)	15
	PEG-32 distearate	Kessco® PEG 1540 DS (Stepan)	15
	PEG-400 dioleate	Cithrol 4DO series (Croda)	>10
	PEG-400 distearate	Cithrol 4DS series (Croda)	>10

15

### 1.3 PEG-Fatty Acid Mono- and Di-ester Mixtures

In general, mixtures of surfactants are also useful in the present invention, including mixtures of two or more commercial surfactant products. Several PEG-fatty acid esters are marketed commercially as mixtures or mono- and diesters. Representative surfactant mixtures are shown in Table 3.

20

Table 3: PEG-Fatty Acid Mono- and Diester Mixtures

	COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
25	PEG 4-150 mono, dilaurate	Kessco® PEG 200-6000 mono, dilaurate (Stepan)	
	PEG 4-150 mono, dioleate	Kessco® PEG 200-6000 mono, dioleate (Stepan)	
	PEG 4-150 mono, distearate	Kessco® 200-6000 mono, distearate (Stepan)	

### 1.4 Polyethylene Glycol Glycerol Fatty Acid Esters

30

Suitable PEG glycerol fatty acid esters are shown in Table 4. Among the surfactants in the Table, preferred hydrophilic surfactants are PEG-20 glyceryl laurate,

1 PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-20 glyceryl oleate, and PEG-30 glyceryl oleate.

Table 4: PEG Glycerol Fatty Acid Esters

5

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-20 glyceryl laurate	Tagat® L (Goldschmidt)	16
PEG-30 glyceryl laurate	Tagat® L2 (Goldschmidt)	16
PEG-15 glyceryl laurate	Glycerox L series (Croda)	15
10 PEG-40 glyceryl laurate	Glycerox L series (Croda)	15
PEG-20 glyceryl stearate	Capmul® EMG (ABITEC), Aldo® MS-20 KFG (Lonza)	13
PEG-20 glyceryl oleate	Tagat® O (Goldschmidt)	>10
PEG-30 glyceryl oleate	Tagat® O2 (Goldschmidt)	>10

15 1.5. Alcohol - Oil Transesterification Products

A large number of surfactants of different degrees of hydrophobicity or hydrophilicity can be prepared by reaction of alcohols or polyalcohols with a variety of natural and/or hydrogenated oils. Most commonly, the oils used are castor oil or hydrogenated castor oil, or an edible vegetable oil such as corn oil, olive oil, peanut oil, palm kernel oil, apricot kernel oil, or almond oil. Preferred alcohols include glycerol, propylene glycol, ethylene glycol, polyethylene glycol, maltol, sorbitol, and pentaerythritol. Among these alcohol-oil transesterified surfactants, preferred hydrophilic surfactants are PEG-35 castor oil (Incrocas-35), PEG-40 hydrogenated castor oil (Cremophor RH 40), PEG-25 trioleate (TAGAT® TO), PEG-60 corn glycerides (Crovol M70), PEG-60 almond oil (Crovol A70), PEG-40 palm kernel oil (Crovol PK70), PEG-50 castor oil (Emalex C-50), PEG-50 hydrogenated castor oil (Emalex HC-50), PEG-8 caprylic/capric glycerides (Labrasol), and PEG-6 caprylic/capric glycerides (Softigen 767). Preferred hydrophobic surfactants in this class include PEG-5 hydrogenated castor oil, PEG-7 hydrogenated castor oil, PEG-9 hydrogenated castor oil, PEG-6 corn oil (Labrafil® M 2125 CS), PEG-6 almond oil (Labrafil® M 1966 CS), PEG-6 apricot kernel oil (Labrafil® M 1944 CS), PEG-6 olive oil (Labrafil® M 1980 CS), PEG-6 peanut oil (Labrafil® M 1969 CS), PEG-6 hydrogenated palm kernel oil (Labrafil® M 2130 BS),

20

25

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1 PEG-6 palm kernel oil (Labrafil® M 2130 CS), PEG-6 triolein (Labrafil® M 2735 CS),  
 PEG-8 corn oil (Labrafil® WL 2609 BS), PEG-20 corn glycerides (Crovol M40), and  
 PEG-20 almond glycerides (Crovol A40). The latter two surfactants are reported to have  
 HLB values of 10, which is generally considered to be the approximate border line  
 5 between hydrophilic and hydrophobic surfactants. For purposes of the present invention,  
 these two surfactants are considered to be hydrophobic. Representative surfactants of this  
 class suitable for use in the present invention are shown in Table 5.

Table 5: Transesterification Products of Oils and Alcohols

10

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-3 castor oil	Nikkol CO-3 (Nikko)	3
PEG-5, 9, and 16 castor oil	ACCONON CA series (ABITEC)	6-7
PEG-20 castor oil	Emalex C-20 (Nihon Emulsion), Nikkol CO-20 TX (Nikko)	11
15 PEG-23 castor oil	Emulgante EL23	>10
PEG-30 castor oil	Emalex C-30 (Nihon Emulsion), Alkamuls® EL 620 (Rhone-Poulenc), Incrocas 30 (Croda)	11
PEG-35 castor oil	Cremophor EL and EL-P (BASF), Emulphor EL, Incrocas-35 (Croda), Emulgin RO 35 (Henkel)	
PEG-38 castor oil	Emulgante EL 65 (Condea)	
20 PEG-40 castor oil	Emalex C-40 (Nihon Emulsion), Alkamuls® EL 719 (Rhone-Poulenc)	13
PEG-50 castor oil	Emalex C-50 (Nihon Emulsion)	14
PEG-56 castor oil	Eumulgin® PRT 56 (Pulcra SA)	>10
PEG-60 castor oil	Nikkol CO-60TX (Nikko)	14
25 PEG-100 castor oil	Thornley	>10
PEG-200 castor oil	Eumulgin® PRT 200 (Pulcra SA)	>10
PEG-5 hydrogenated castor oil	Nikkol HCO-5 (Nikko)	6
PEG-7 hydrogenated castor oil	Simusol® 989 (Seppic), Cremophor WO7 (BASF)	6
PEG-10 hydrogenated castor oil	Nikkol HCO-10 (Nikko)	6.5
30 PEG-20 hydrogenated castor oil	Nikkol HCO-20 (Nikko)	11
PEG-25 hydrogenated castor oil	Simulsol® 1292 (Seppic), Cerex ELS 250 (Auschem SpA)	11
PEG-30 hydrogenated castor oil	Nikkol HCO-30 (Nikko)	11

1	PEG-40 hydrogenated castor oil	Cremophor RH 40 (BASF), Croduret (Croda), Emulgin HRE 40 (Henkel)	13
	PEG-45 hydrogenated castor oil	Cerex ELS 450 (Auschem Spa)	14
	PEG-50 hydrogenated castor oil	Emalex HC-50 (Nihon Emulsion)	14
5	PEG-60 hydrogenated castor oil	Nikkol HCO-60 (Nikko); Cremophor RH 60 (BASF)	15
	PEG-80 hydrogenated castor oil	Nikkol HCO-80 (Nikko)	15
	PEG-100 hydrogenated castor oil	Nikkol HCO -100 (Nikko)	17
	PEG-6 corn oil	Labrafil® M 2125 CS (Gattefosse)	4
10	PEG-6 almond oil	Labrafil® M 1966 CS (Gattefosse)	4
	PEG-6 apricot kernel oil	Labrafil® M 1944 CS (Gattefosse)	4
	PEG-6 olive oil	Labrafil® M 1980 CS (Gattefosse)	4
	PEG-6 peanut oil	Labrafil® M 1969 CS (Gattefosse)	4
	PEG-6 hydrogenated palm kernel oil	Labrafil® M 2130 BS (Gattefosse)	4
15	PEG-6 palm kernel oil	Labrafil® M 2130 CS (Gattefosse)	4
	PEG-6 triolein	Labrafil® M 2735 CS (Gattefosse)	4
	PEG-8 corn oil	Labrafil® WL 2609 BS (Gattefosse)	6-7
	PEG-20 corn glycerides	Crovol M40 (Croda)	10
20	PEG-20 almond glycerides	Crovol A40 (Croda)	10
	PEG-25 trioleate	TAGAT® TO (Goldschmidt)	11
	PEG-40 palm kernel oil	Crovol PK-70	>10
	PEG-60 corn glycerides	Crovol M70 (Croda)	15
	PEG-60 almond glycerides	Crovol A70 (Croda)	15
25	PEG-4 caprylic/capric triglyceride	Labrafac® Hydro (Gattefosse),	4-5
	PEG-8 caprylic/capric glycerides	Labrasol (Gattefosse), Labrafac CM 10 (Gattefosse)	>10
	PEG-6 caprylic/capric glycerides	SOFTIGEN® 767 (Hüls), Glycerox 767 (Croda)	19
	Lauroyl macrogol-32 glyceride	GELUCIRE 44/14 (Gattefosse)	14
30	Stearoyl macrogol glyceride	GELUCIRE 50/13 (Gattefosse)	13
	Mono, di, tri, tetra esters of vegetable oils and sorbitol	SorbitoGlyceride (Gattefosse)	<10
	Pentaerythrityl tetraisostearate	Crodamol PTIS (Croda)	<10

1	Pentaerythrityl distearate	Albunol DS (Taiwan Surf.)	<10
	Pentaerythrityl tetraoleate	Liponate PO-4 (Lipo Chem.)	<10
	Pentaerythrityl tetrastearate	Liponate PS-4 (Lipo Chem.)	<10
5	Pentaerythrityl tetracaprylate/tetracaprate	Liponate PE-810 (Lipo Chem.), Crodamol PTC (Croda)	<10
	Pentaerythrityl tetraoctanoate	Nikkol Pentarate 408 (Nikko)	

Also included as oils in this category of surfactants are oil-soluble vitamins, such as vitamins A, D, E, K, etc. Thus, derivatives of these vitamins, such as tocopheryl PEG-1000 succinate (TPGS, available from Eastman), are also suitable surfactants.

#### 1.6. Polyglycerized Fatty Acids

Polyglycerol esters of fatty acids are also suitable surfactants for the present invention. Among the polyglyceryl fatty acid esters, preferred hydrophobic surfactants include polyglyceryl oleate (Plurol Oleique), polyglyceryl-2 dioleate (Nikkol DGDO), and polyglyceryl-10 trioleate. Preferred hydrophilic surfactants include polyglyceryl-10 laurate (Nikkol Decaglyn 1-L), polyglyceryl-10 oleate (Nikkol Decaglyn 1-O), and polyglyceryl-10 mono, dioleate (Caprol® PEG 860). Polyglyceryl polyricinoleates (Polymuls) are also preferred hydrophilic and hydrophobic surfactants. Examples of suitable polyglyceryl esters are shown in Table 6.

Table 6: Polyglycerized Fatty Acids

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Polyglyceryl-2 stearate	Nikkol DGMS (Nikko)	5-7
25 Polyglyceryl-2 oleate	Nikkol DGMO (Nikko)	5-7
Polyglyceryl-2 isostearate	Nikkol DGMIS (Nikko)	5-7
Polyglyceryl-3 oleate	Caprol® 3GO (ABITEC), Drewpol 3-1-O (Stepan)	6.5
Polyglyceryl-4 oleate	Nikkol Tetraglyn 1-O (Nikko)	5-7
Polyglyceryl-4 stearate	Nikkol Tetraglyn 1-S (Nikko)	5-6
30 Polyglyceryl-6 oleate	Drewpol 6-1-O (Stepan), Nikkol Hexaglyn 1-O (Nikko)	9
Polyglyceryl-10 laurate	Nikkol Decaglyn 1-L (Nikko)	15
Polyglyceryl-10 oleate	Nikkol Decaglyn 1-O (Nikko)	14

1	Polyglyceryl-10 stearate	Nikkol Decaglyn 1-S (Nikko)	12
	Polyglyceryl-6 ricinoleate	Nikkol Hexaglyn PR-15 (Nikko)	>8
	Polyglyceryl-10 linoleate	Nikkol Decaglyn 1-LN (Nikko)	12
5	Polyglyceryl-6 pentaoleate	Nikkol Hexaglyn 5-O (Nikko)	<10
	Polyglyceryl-3 dioleate	Cremophor GO32 (BASF)	<10
	Polyglyceryl-3 distearate	Cremophor GS32 (BASF)	<10
	Polyglyceryl-4 pentaoleate	Nikkol Tetraglyn 5-O (Nikko)	<10
	Polyglyceryl-6 dioleate	Caprol® 6G20 (ABITEC); Hodag PGO-62 (Calgene), PLUROL OLEIQUE CC 497 (Gattefosse)	8.5
10	Polyglyceryl-2 dioleate	Nikkol DGDO (Nikko)	7
	Polyglyceryl-10 trioleate	Nikkol Decaglyn 3-O (Nikko)	7
	Polyglyceryl-10 pentaoleate	Nikkol Decaglyn 5-O (Nikko)	3.5
	Polyglyceryl-10 septaoleate	Nikkol Decaglyn 7-O (Nikko)	3
15	Polyglyceryl-10 tetraoleate	Caprol® 10G4O (ABITEC); Hodag PGO-62 (CALGENE), Drewpol 10-4-O (Stepan)	6.2
	Polyglyceryl-10 decaisostearate	Nikkol Decaglyn 10-IS (Nikko)	<10
	Polyglyceryl-10l decaoleate	Drewpol 10-10-O (Stepan), Caprol 10G10O (ABITEC), Nikkol Decaglyn 10-O	3.5
	Polyglyceryl-10 mono, dioleate	Caprol® PGE 860 (ABITEC)	11
20	Polyglyceryl polyricinoleate	Polymuls (Henkel)	3-20

### 1.7. Propylene Glycol Fatty Acid Esters

Esters of propylene glycol and fatty acids are suitable surfactants for use in the present invention. In this surfactant class, preferred hydrophobic surfactants include  
 25 propylene glycol monolaurate (Lauroglycol FCC), propylene glycol ricinoleate (Propymuls), propylene glycol monooleate (Myverol P-O6), propylene glycol dicaprylate/dicaprate (Captex® 200), and propylene glycol dioctanoate (Captex® 800). Examples of surfactants of this class are given in Table 7.

Table 7: Propylene Glycol Fatty Acid Esters

	COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
	Propylene glycol monocaprylate	Capryol 90 (Gattefosse), Nikkol Sefsol 218 (Nikko)	<10
5	Propylene glycol monolaurate	Lauroglycol 90 (Gattefosse), Lauroglycol FCC (Gattefosse)	<10
	Propylene glycol oleate	Lutrol OP2000 (BASF)	<10
	Propylene glycol myristate	Mirpyl	<10
	Propylene glycol monostearate	ADM PGME-03 (ADM), LIPO PGMS (Lipo Chem.), Aldo® PGHMS (Lonza)	3-4
10	Propylene glycol hydroxy stearate		<10
	Propylene glycol ricinoleate	PROPYMULS (Henkel)	<10
	Propylene glycol isostearate		<10
	Propylene glycol monooleate	Myverol P-O6 (Eastman)	<10
	Propylene glycol dicaprylate/dicaprate	Captex® 200 (ABITEC), Miglyol® 840 (Hüls), Neobee® M-20 (Stepan)	>6
15	Propylene glycol dioctanoate	Captex® 800 (ABITEC)	>6
	Propylene glycol caprylate/caprate	LABRAFAC PG (Gattefosse)	>6
	Propylene glycol dilaurate		>6
	Propylene glycol distearate	Kessco® PGDS (Stepan)	>6
20	Propylene glycol dicaprylate	Nikkol Sefsol 228 (Nikko)	>6
	Propylene glycol dicaprate	Nikkol PDD (Nikko)	>6

Table 7 includes both mono- and diesters of propylene glycol, and both may be used in one embodiment of the pharmaceutical systems of the present invention. In another embodiment, the absorption enhancing composition is free of both triglycerides and propylene glycol diesters.

#### 1.8. Mixtures of Propylene Glycol Esters - Glycerol Esters

In general, mixtures of surfactants are also suitable for use in the present invention. In particular, mixtures of propylene glycol fatty acid esters and glycerol fatty acid esters are suitable and are commercially available. One preferred mixture is composed of the oleic acid esters of propylene glycol and glycerol (Arlacel 186). Examples of these surfactants are shown in Table 8.



Table 8: Glycerol/Propylene Glycol Fatty Acid Esters

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Oleic	ATMOS 300, ARLACEL 186 (ICI)	3-4
Stearic	ATMOS 150	3-4

### 1.9. Mono- and Diglycerides

A particularly important class of surfactants is the class of mono- and diglycerides. These surfactants are generally hydrophobic. Preferred hydrophobic surfactants in this class of compounds include glyceryl monooleate (Peceol), glyceryl ricinoleate, glyceryl laurate, glyceryl dilaurate (Capmul® GDL), glyceryl dioleate (Capmul® GDO), glyceryl mono/dioleate (Capmul® GMO-K), glyceryl caprylate/caprate (Capmul® MCM), caprylic acid mono/diglycerides (Imwitor® 988), and mono- and diacetylated monoglycerides (Myvacet® 9-45). Examples of these surfactants are given in Table 9.

Table 9: Mono- and Diglyceride Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Monopalmitolein (C16:1)	(Larodan)	<10
Monoelaidin (C18:1)	(Larodan)	<10
Monocaproin (C6)	(Larodan)	<10
Monocaprylin	(Larodan)	<10
Monocaprin	(Larodan)	<10
Monolaurin	(Larodan)	<10
Glyceryl monomyristate (C14)	Nikkol MGM (Nikko)	3-4
Glyceryl monooleate (C18:1)	PECEOL (Gattefosse), Hodag GMO-D, Nikkol MGO (Nikko)	3-4
Glyceryl monooleate	RYLO series (Danisco), DIMODAN series (Danisco), EMULDAN (Danisco), ALDO® MO FG (Lonza), Kessco GMO (Stepan), MONOMULS® series (Henkel), TEGIN O, DREWMULSE GMO (Stepan), Atlas G-695 (ICI), GMOorphic 80 (Eastman), ADM DMG-40, 70, and 100 (ADM), Myverol (Eastman)	3-4
Glycerol monooleate/linoleate	OLICINE (Gattefosse)	3-4

1	Glycerol monolinoleate	Maisine (Gattefosse), MYVEROL 18-92, Myverol 18-06 (Eastman)	3-4
	Glyceryl ricinoleate	Softigen® 701 (Hüls), HODAG GMR-D (Calgene), ALDO® MR (Lonza)	6
	Glyceryl monolaurate	ALDO® MLD (Lonza), Hodag GML (Calgene)	6.8
5	Glycerol monopalmitate	Emalex GMS-P (Nihon)	4
	Glycerol monostearate	Capmul® GMS (ABITEC), Myvaplex (Eastman), IMWITOR® 191 (Hüls), CUTINA GMS, Aldo® MS (Lonza), Nikkol MGS series (Nikko)	5-9
	Glyceryl mono-,dioleate	Capmul® GMO-K (ABITEC)	<10
	Glyceryl palmitic/stearic	CUTINA MD-A, ESTAGEL-G18	<10
10	Glyceryl acetate	Lamegin® EE (Grünau GmbH)	<10
	Glyceryl laurate	Imwitor® 312 (Hüls), Monomuls® 90-45 (Grünau GmbH), Aldo® MLD (Lonza)	4
	Glyceryl citrate/lactate/oleate/ linoleate	Imwitor® 375 (Hüls)	<10
15	Glyceryl caprylate	Imwitor® 308 (Hüls), Capmul® MCMC8 (ABITEC)	5-6
	Glyceryl caprylate/caprate	Capmul® MCM (ABITEC)	5-6
	Caprylic acid mono,diglycerides	Imwitor® 988 (Hüls)	5-6
	Caprylic/capric glycerides	Imwitor® 742 (Hüls)	<10
	Mono-and diacetylated monoglycerides	Myvacet® 9-45, Myvacet® 9-40, Myvacet® 9-08 (Eastman), Lamegin® (Grünau)	3.8-4
20	Glyceryl monostearate	Aldo® MS, Arlacel 129 (ICI), LIPO GMS (Lipo Chem.), Imwitor® 191 (Hüls), Myvaplex (Eastman)	4.4
	Lactic acid esters of mono,diglycerides	LAMEGIN GLP (Henkel)	<10
	Dicaproin (C6)	(Larodan)	<10
25	Dicaprin (C10)	(Larodan)	<10
	Diocetanoin (C8)	(Larodan)	<10
	Dimyristin (C14)	(Larodan)	<10
	Dipalmitin (C16)	(Larodan)	<10
	Distearin	(Larodan)	<10
30	Glyceryl dilaurate (C12)	Capmul® GDL (ABITEC)	3-4
	Glyceryl dioleate	Capmul® GDO (ABITEC)	3-4
	Glycerol esters of fatty acids	GELUCIRE 39/01 (Gattefosse), GELUCIRE 43/01 (Gattefosse)	1

1		GELUCIRE 37/06 (Gattefosse)	6
	Dipalmitolein (C16:1)	(Larodan)	<10
	1,2 and 1,3-diolein (C18:1)	(Larodan)	<10
5	Dielaidin (C18:1)	(Larodan)	<10
	Dilinolein (C18:2)	(Larodan)	<10

#### 1.10. Sterol and Sterol Derivatives

10 Sterols and derivatives of sterols are suitable surfactants for use in the present invention. These surfactants can be hydrophilic or hydrophobic. Preferred derivatives include the polyethylene glycol derivatives. A preferred hydrophobic surfactant in this class is cholesterol. A preferred hydrophilic surfactant in this class is PEG-24 cholesterol ether (Solulan C-24). Examples of surfactants of this class are shown in Table 10.

15 Table 10: Sterol and Sterol Derivative Surfactants

	COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
	Cholesterol, sitosterol, lanosterol		<10
	PEG-24 cholesterol ether	Solulan C-24 (Amerchol)	>10
20	PEG-30 cholestanol	Nikkol DHC (Nikko)	>10
	Phytosterol	GENEROL series (Henkel)	<10
	PEG-25 phyto sterol	Nikkol BPSH-25 (Nikko)	>10
	PEG-5 soya sterol	Nikkol BPS-5 (Nikko)	<10
	PEG-10 soya sterol	Nikkol BPS-10 (Nikko)	<10
25	PEG-20 soya sterol	Nikkol BPS-20 (Nikko)	<10
	PEG-30 soya sterol	Nikkol BPS-30 (Nikko)	>10

#### 1.11. Polyethylene Glycol Sorbitan Fatty Acid Esters

30 A variety of PEG-sorbitan fatty acid esters are available and are suitable for use as surfactants in the present invention. In general, these surfactants are hydrophilic, although several hydrophobic surfactants of this class can be used. Among the PEG-sorbitan fatty acid esters, preferred hydrophilic surfactants include PEG-20 sorbitan monolaurate

1 (Tween-20), PEG-20 sorbitan monopalmitate (Tween-40), PEG-20 sorbitan monostearate  
(Tween-60), and PEG-20 sorbitan monooleate (Tween-80). Examples of these surfactants  
are shown in Table 11.

5 Table 11: PEG-Sorbitan Fatty Acid Esters

	COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
	PEG-10 sorbitan laurate	Liposorb L-10 (Lipo Chem.)	>10
	PEG-20 sorbitan monolaurate	Tween-20 (Atlas/ICI), Crillet 1 (Croda), DACOL MLS 20 (Condea)	17
10	PEG-4 sorbitan monolaurate	Tween-21 (Atlas/ICI), Crillet 11 (Croda)	13
	PEG-80 sorbitan monolaurate	Hodag PSML-80 (Calgene); T-Maz 28	>10
	PEG-6 sorbitan monolaurate	Nikkol GL-1 (Nikko)	16
	PEG-20 sorbitan monopalmitate	Tween-40 (Atlas/ICI), Crillet 2 (Croda)	16
	PEG-20 sorbitan monostearate	Tween-60 (Atlas/ICI), Crillet 3 (Croda)	15
15	PEG-4 sorbitan monostearate	Tween-61 (Atlas/ICI), Crillet 31 (Croda)	9.6
	PEG-8 sorbitan monostearate	DACOL MSS (Condea)	>10
	PEG-6 sorbitan monostearate	Nikkol TS106 (Nikko)	11
	PEG-20 sorbitan tristearate	Tween-65 (Atlas/ICI), Crillet 35 (Croda)	11
	PEG-6 sorbitan tetrastearate	Nikkol GS-6 (Nikko)	3
20	PEG-60 sorbitan tetrastearate	Nikkol GS-460 (Nikko)	13
	PEG-5 sorbitan monooleate	Tween-81 (Atlas/ICI), Crillet 41 (Croda)	10
	PEG-6 sorbitan monooleate	Nikkol TO-106 (Nikko)	10
	PEG-20 sorbitan monooleate	Tween-80 (Atlas/ICI), Crillet 4 (Croda)	15
	PEG-40 sorbitan oleate	Emalex ET 8040 (Nihon Emulsion)	18
25	PEG-20 sorbitan trioleate	Tween-85 (Atlas/ICI), Crillet 45 (Croda)	11
	PEG-6 sorbitan tetraoleate	Nikkol GO-4 (Nikko)	8.5
	PEG-30 sorbitan tetraoleate	Nikkol GO-430 (Nikko)	12
	PEG-40 sorbitan tetraoleate	Nikkol GO-440 (Nikko)	13
30	PEG-20 sorbitan monoisostearate	Tween-120 (Atlas/ICI), Crillet 6 (Croda)	>10
	PEG sorbitol hexaoleate	Atlas G-1086 (ICI)	10
	PEG-6 sorbitol hexastearate	Nikkol GS-6 (Nikko)	3

### 1.12. Polyethylene Glycol Alkyl Ethers

Ethers of polyethylene glycol and alkyl alcohols are suitable surfactants for use in the present invention. Preferred hydrophobic ethers include PEG-3 oleyl ether (Volpo 3) and PEG-4 lauryl ether (Brij 30). Examples of these surfactants are shown in Table 12.

Table 12: Polyethylene Glycol Alkyl Ethers

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-2 oleyl ether, oleth-2	Brij 92/93 (Atlas/ICI)	4.9
PEG-3 oleyl ether, oleth-3	Volpo 3 (Croda)	<10
PEG-5 oleyl ether, oleth-5	Volpo 5 (Croda)	<10
PEG-10 oleyl ether, oleth-10	Volpo 10 (Croda), Brij 96/97 (Atlas/ICI)	12
PEG-20 oleyl ether, oleth-20	Volpo 20 (Croda), Brij 98/99 (Atlas/ICI)	15
PEG-4 lauryl ether, laureth-4	Brij 30 (Atlas/ICI)	9.7
PEG-9 lauryl ether		>10
PEG-23 lauryl ether, laureth-23	Brij 35 (Atlas/ICI)	17
PEG-2 cetyl ether	Brij 52 (ICI)	5.3
PEG-10 cetyl ether	Brij 56 (ICI)	13
PEG-20 cetyl ether	Brij 58 (ICI)	16
PEG-2 stearyl ether	Brij 72 (ICI)	4.9
PEG-10 stearyl ether	Brij 76 (ICI)	12
PEG-20 stearyl ether	Brij 78 (ICI)	15
PEG-100 stearyl ether	Brij 700 (ICI)	>10

### 1.13. Sugar Esters

Esters of sugars are suitable surfactants for use in the present invention. Preferred hydrophilic surfactants in this class include sucrose monopalmitate and sucrose monolaurate. Examples of such surfactants are shown in Table 13.



Table 13: Sugar Ester Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Sucrose distearate	SUCRO ESTER 7 (Gattefosse), Crodesta F-10 (Croda)	3
Sucrose distearate/monostearate	SUCRO ESTER 11 (Gattefosse), Crodesta F-110 (Croda)	12
Sucrose dipalmitate		7.4
Sucrose monostearate	Crodesta F-160 (Croda)	15
Sucrose monopalmitate	SUCRO ESTER 15 (Gattefosse)	>10
Sucrose monolaurate	Saccharose monolaurate 1695 (Mitsubishi-Kasei)	15

## 1.14. Polyethylene Glycol Alkyl Phenols

Several hydrophilic PEG-alkyl phenol surfactants are available, and are suitable for use in the present invention. Examples of these surfactants are shown in Table 14.

Table 14: Polyethylene Glycol Alkyl Phenol Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
PEG-10-100 nonyl phenol	Triton X series (Rohm & Haas), Igepal CA series (GAF, USA), Antarox CA series (GAF, UK)	>10
PEG-15-100 octyl phenol ether	Triton N-series (Rohm & Haas), Igepal CO series (GAF, USA), Antarox CO series (GAF, UK)	>10

## 1.15. Polyoxyethylene-Polyoxypropylene Block Copolymers

The POE-POP block copolymers are a unique class of polymeric surfactants. The unique structure of the surfactants, with hydrophilic POE and hydrophobic POP moieties in well-defined ratios and positions, provides a wide variety of surfactants suitable for use in the present invention. These surfactants are available under various trade names, including Synperonic PE series (ICI); Pluronic® series (BASF), Emkalyx, Lutrol (BASF), Supronic, Monolan, Pluracare, and Pluradac. The generic term for these polymers is "poloxamer" (CAS 9003-11-6). These polymers have the formula:



where "a" and "b" denote the number of polyoxyethylene and polyoxypropylene units, respectively.

1 Preferred hydrophilic surfactants of this class include Poloxamers 108, 188, 217, 238, 288, 338, and 407. Preferred hydrophobic surfactants in this class include Poloxamers 124, 182, 183, 212, 331, and 335.

5 Examples of suitable surfactants of this class are shown in Table 15. Since the compounds are widely available, commercial sources are not listed in the Table. The compounds are listed by generic name, with the corresponding "a" and "b" values.

Table 15: POE-POP Block Copolymers

COMPOUND	a, b values in $\text{HO}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})_a\text{H}$	HLB
10 Poloxamer 105	a = 11 b = 16	8
Poloxamer 108	a = 46 b = 16	>10
Poloxamer 122	a = 5 b = 21	3
Poloxamer 123	a = 7 b = 21	7
Poloxamer 124	a = 11 b = 21	>7
15 Poloxamer 181	a = 3 b = 30	
Poloxamer 182	a = 8 b = 30	2
Poloxamer 183	a = 10 b = 30	
Poloxamer 184	a = 13 b = 30	
Poloxamer 185	a = 19 b = 30	
20 Poloxamer 188	a = 75 b = 30	29
Poloxamer 212	a = 8 b = 35	
Poloxamer 215	a = 24 b = 35	
Poloxamer 217	a = 52 b = 35	
Poloxamer 231	a = 16 b = 39	
Poloxamer 234	a = 22 b = 39	
25 Poloxamer 235	a = 27 b = 39	
Poloxamer 237	a = 62 b = 39	24
Poloxamer 238	a = 97 b = 39	
Poloxamer 282	a = 10 b = 47	
Poloxamer 284	a = 21 b = 47	
30 Poloxamer 288	a = 122 b = 47	>10
Poloxamer 331	a = 7 b = 54	0.5
Poloxamer 333	a = 20 b = 54	
Poloxamer 334	a = 31 b = 54	

1	Poloxamer 335	a = 38	b = 54
	Poloxamer 338	a = 128	b = 54
	Poloxamer 401	a = 6	b = 67
	Poloxamer 402	a = 13	b = 67
5	Poloxamer 403	a = 21	b = 67
	Poloxamer 407	a = 98	b = 67

#### 1.16. Sorbitan Fatty Acid Esters

10 Sorbitan esters of fatty acids are suitable surfactants for use in the present invention. Among these esters, preferred hydrophobic surfactants include sorbitan monolaurate (Arlacel 20), sorbitan monopalmitate (Span-40), sorbitan monooleate (Span-80), sorbitan monostearate, and sorbitan tristearate. Examples of these surfactants are shown in Table 16.

Table 16: Sorbitan Fatty Acid Ester Surfactants

15	COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
	Sorbitan monolaurate	Span-20 (Atlas/ICI), Crill 1 (Croda), Arlacel 20 (ICI)	8.6
	Sorbitan monopalmitate	Span-40 (Atlas/ICI), Crill 2 (Croda), Nikkol SP-10 (Nikko)	6.7
	Sorbitan monooleate	Span-80 (Atlas/ICI), Crill 4 (Croda), Crill 50 (Croda)	4.3
20	Sorbitan monostearate	Span-60 (Atlas/ICI), Crill 3 (Croda), Nikkol SS-10 (Nikko)	4.7
	Sorbitan trioleate	Span-85 (Atlas/ICI), Crill 45 (Croda), Nikkol SO-30 (Nikko)	4.3
	Sorbitan sesquioleate	Arlacel-C (ICI), Crill 43 (Croda), Nikkol SO-15 (Nikko)	3.7
	Sorbitan tristearate	Span-65 (Atlas/ICI) Crill 35 (Croda), Nikkol SS-30 (Nikko)	2.1
	Sorbitan monoisostearate	Crill 6 (Croda), Nikkol SI-10 (Nikko)	4.7
25	Sorbitan sesquisteate	Nikkol SS-15 (Nikko)	4.2

#### 1.17. Lower Alcohol Fatty Acid Esters

30 Esters of lower alcohols ( $C_2$  to  $C_4$ ) and fatty acids ( $C_8$  to  $C_{18}$ ) are suitable surfactants for use in the present invention. Among these esters, preferred hydrophobic surfactants include ethyl oleate (Crodamol EO), isopropyl myristate (Crodamol IPM), and isopropyl palmitate (Crodamol IPP). Examples of these surfactants are shown in Table 17.

1

Table 17: Lower Alcohol Fatty Acid Ester Surfactants

COMPOUND	COMMERCIAL PRODUCT (Supplier)	HLB
Ethyl oleate	Crodamol EO (Croda), Nikkol EOO (Nikko)	<10
Isopropyl myristate	Crodamol IPM (Croda)	<10
5 Isopropyl palmitate	Crodamol IPP (Croda)	<10
Ethyl linoleate	Nikkol VF-E (Nikko)	<10
Isopropyl linoleate	Nikkol VF-IP (Nikko)	<10

## 1.18. Ionic Surfactants

10

15

20

Ionic surfactants, including cationic, anionic and zwitterionic surfactants, are suitable hydrophilic surfactants for use in the present invention. Preferred anionic surfactants include fatty acid salts and bile salts. Preferred cationic surfactants include carnitines. Specifically, preferred ionic surfactants include sodium oleate, sodium lauryl sulfate, sodium lauryl sarcosinate, sodium dioctyl sulfosuccinate, sodium cholate, sodium taurocholate; lauroyl carnitine; palmitoyl carnitine; and myristoyl carnitine. Examples of such surfactants are shown in Table 18. For simplicity, typical counterions are shown in the entries in the Table. It will be appreciated by one skilled in the art, however, that any bioacceptable counterion may be used. For example, although the fatty acids are shown as sodium salts, other cation counterions can also be used, such as alkali metal cations or ammonium. Unlike typical non-ionic surfactants, these ionic surfactants are generally available as pure compounds, rather than commercial (proprietary) mixtures. Because these compounds are readily available from a variety of commercial suppliers, such as Aldrich, Sigma, and the like, commercial sources are not generally listed in the Table.

25

Table 18: Ionic Surfactants

COMPOUND	HLB
<b>FATTY ACID SALTS</b>	<b>&gt;10</b>
Sodium caproate	
Sodium caprylate	
Sodium caprate	
30 Sodium laurate	
Sodium myristate	
Sodium myristolate	
Sodium palmitate	
Sodium palmitoleate	

1	Sodium oleate	18
	Sodium ricinoleate	
	Sodium linoleate	
	Sodium linolenate	
	Sodium stearate	
5	Sodium lauryl sulfate (dodecyl)	40
	Sodium tetradecyl sulfate	
	Sodium lauryl sarcosinate	
	Sodium dioctyl sulfosuccinate [sodium docusate (Cytec)]	
	<b>BILE SALTS</b>	>10
	Sodium cholate	
	Sodium taurocholate	
10	Sodium glycocholate	
	Sodium deoxycholate	
	Sodium taurodeoxycholate	
	Sodium glycodeoxycholate	
	Sodium ursodeoxycholate	
	Sodium chenodeoxycholate	
15	Sodium taurochenodeoxycholate	
	Sodium glyco cheno deoxycholate	
	Sodium cholylsarcosinate	
	Sodium N-methyl taurocholate	
	Sodium lithocholate	
	<b>PHOSPHOLIPIDS</b>	
	Egg/Soy lecithin [Epikuron™ (Lucas Meyer), Ovothin™ (Lucas Meyer)]	
20	Lyso egg/soy lecithin	
	Hydroxylated lecithin	
	Lysophosphatidylcholine	
	Cardiolipin	
	Sphingomyelin	
	Phosphatidylcholine	
	Phosphatidyl ethanolamine	
25	Phosphatidic acid	
	Phosphatidyl glycerol	
	Phosphatidyl serine	
	<b>PHOSPHORIC ACID ESTERS</b>	
	Diethanolammonium polyoxyethylene-10 oleyl ether phosphate	
	Esterification products of fatty alcohols or fatty alcohol ethoxylates with phosphoric acid or anhydride	
30	<b>CARBOXYLATES</b>	
	Ether carboxylates (by oxidation of terminal OH group of fatty alcohol ethoxylates)	
	Succinylated monoglycerides [LAMEGIN ZE (Henkel)]	

- 1 Sodium stearyl fumarate  
 Stearoyl propylene glycol hydrogen succinate  
 Mono/diacetylated tartaric acid esters of mono- and diglycerides  
 Citric acid esters of mono-, diglycerides  
 Glyceryl-lacto esters of fatty acids (CFR ref. 172.852)
- 5 Acyl lactylates:  
     lactylic esters of fatty acids  
     calcium/sodium stearoyl-2-lactylate  
     calcium/sodium stearoyl lactylate
- Alginate salts  
 Propylene glycol alginate
- SULFATES AND SULFONATES**
- 10 Ethoxylated alkyl sulfates  
 Alkyl benzene sulfones  
 $\alpha$ -olefin sulfonates  
 Acyl isethionates  
 Acyl taurates  
 Alkyl glyceryl ether sulfonates  
 Octyl sulfosuccinate disodium
- 15 Disodium undecylenamideo-MEA-sulfosuccinate
- CATIONIC Surfactants** >10
- Lauroyl carnitine  
 Palmitoyl carnitine  
 Myristoyl carnitine  
 Hexadecyl triammonium bromide  
 Decyl trimethyl ammonium bromide
- 20 Cetyl trimethyl ammonium bromide  
 Dodecyl ammonium chloride  
 Alkyl benzyldimethylammonium salts  
 Diisobutyl phenoxyethoxydimethyl benzylammonium salts  
 Alkylpyridinium salts  
 Betaines (trialkylglycine):  
     Lauryl betaine (N-lauryl,N,N-dimethylglycine)
- 25 Ethoxylated amines:  
     Polyoxyethylene-15 coconut amine
- 

### 1.19 Ionizable Surfactants

30 Ionizable surfactants, when present in their un-ionized (neutral, non-salt) form, are hydrophobic surfactants suitable for use in the compositions and methods of the present invention, and in their ionized form, are hydrophilic surfactants suitable for use in the present invention. Particular examples of such surfactants include free fatty acids, particularly C<sub>6</sub>-C<sub>22</sub> fatty acids, and bile acids. More specifically, suitable unionized



1 ionizable surfactants include the free fatty acid and bile acid forms of any of the fatty acid  
salts and bile salts shown in Table 18. Preferred ionizable surfactants include fatty acids  
and their corresponding salts, such as caprylic acid/sodium caprylate, oleic acid/sodium  
oleate, capric acid/sodium caprate; ricinoleic acid/sodium ricinoleate, linoleic acid/sodium  
5 linoleate, and lauric acid/sodium laurate; trihydroxy bile acids and their salts, such as  
cholic acid (natural), glycocholic acid and taurocholic acid; dihydroxy bile acids and their  
salts, such as deoxycholic acid (natural), glycodeoxycholic acid, taurodeoxycholic acid,  
chenodeoxycholic acid (natural), glycochenodeoxycholic acid, taurochenodeoxycholic  
acid, ursodeoxycholic acid, tauroursodeoxycholic acid, and glycoursodeoxycholic acid;  
10 monohydroxy bile acids and their salts, such as lithocholic acid (natural); sulfated bile salt  
derivatives; sarchocholate; fusidic acid and its derivatives; phospholipids, such as  
phosphatidyl choline, phosphatidyl ethanolamine, phosphatidyl serine, PD inisitol,  
lysolecithin, and palmitoyl lysophosphatidyl choline; carnitines, such as palmitoyl  
carnitine, lauroyl carnitine and myristoyl carnitine; cyclodextrins, including alpha, beta  
15 and gamma cyclodextrins; and modified cyclodextrins, such as hydroxy propyl and  
sulfobutyl ether.

#### 1.20 Preferred Surfactants and Surfactant Combinations

Among the above-listed surfactants, several combinations are preferred. In all of  
the preferred combinations, the absorption enhancing composition includes at least one  
20 hydrophilic surfactant. Preferred non-ionic hydrophilic surfactants include  
alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides;  
polyoxyethylene alkyl ethers; polyoxyethylene alkylphenols; polyethylene glycol fatty  
acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty  
acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid  
25 esters; polyoxyethylene glycerides; polyoxyethylene sterols, derivatives, and analogues  
thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils;  
reaction mixtures of polyols with fatty acids, glycerides, vegetable oils, hydrogenated  
vegetable oils, and sterols; sugar esters, sugar ethers; sucroglycerides; and mixtures  
thereof.

30 More preferably, the non-ionic hydrophilic surfactant is selected from the group  
consisting of polyoxyethylene alkylethers; polyethylene glycol fatty acids esters;  
polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters;

1 polyoxyethylene-polyoxypropylene block copolymers; polyglyceryl fatty acid esters; polyoxyethylene glycerides; polyoxyethylene vegetable oils; and polyoxyethylene hydrogenated vegetable oils. The glyceride can be a monoglyceride, diglyceride, triglyceride, or a mixture.

5 Also preferred are non-ionic hydrophilic surfactants that are reaction mixtures of polyols and fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils or sterols. These reaction mixtures are largely composed of the transesterification products of the reaction, along with often complex mixtures of other reaction products. The polyol is preferably glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, 10 pentaerythritol, or a saccharide.

Several particularly preferred absorption enhancing compositions are those which include as a non-ionic hydrophilic surfactant PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, 15 PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated 20 castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl 25 PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10 oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, or a poloxamer.

Among these preferred surfactants, more preferred are PEG-20 laurate, PEG-20 oleate, PEG-35 castor oil, PEG-40 palm kernel oil, PEG-40 hydrogenated castor oil, PEG- 30 60 corn oil, PEG-25 glyceryl trioleate, polyglyceryl-10 laurate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, PEG-30 cholesterol, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, PEG-24

1 cholesterol, sucrose monostearate, sucrose monolaurate and poloxamers. Most preferred  
are PEG-35 castor oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl  
trioleate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides,  
polysorbate 20, polysorbate 80, tocopheryl PEG-1000 succinate, PEG-24 cholesterol, and  
5 hydrophilic poloxamers.

The hydrophilic surfactant can also be, or include as a component, an ionic  
surfactant, *i.e.*, the ionized form of an ionizable surfactant. Preferred ionic surfactants  
include the ionized form of alkyl ammonium salts; bile acids and salts, analogues, and  
derivatives thereof; fusidic acid and derivatives thereof; fatty acid derivatives of amino  
10 acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides,  
and polypeptides; acyl lactylates; mono-,diacetylated tartaric acid esters of mono-  
,diglycerides; succinylated monoglycerides; citric acid esters of mono-,diglycerides;  
alginate salts; propylene glycol alginate; lecithins and hydrogenated lecithins; lysolecithin  
and hydrogenated lysolecithins; lysophospholipids and derivatives thereof; phospholipids  
15 and derivatives thereof; salts of alkylsulfates; salts of fatty acids; sodium docusate;  
carnitines; and mixtures thereof.

More preferable ionized ionizable surfactants include the ionized form of bile acids  
and salts, analogues, and derivatives thereof; lecithins, lysolecithin, phospholipids,  
lysophospholipids and derivatives thereof; salts of alkylsulfates; salts of fatty acids;  
20 sodium docusate; acyl lactylates; mono-,diacetylated tartaric acid esters of mono-  
,diglycerides; succinylated monoglycerides; citric acid esters of mono-,diglycerides;  
carnitines; and mixtures thereof.

More specifically, preferred ionized ionizable surfactants are the ionized forms of  
lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine,  
25 phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine,  
lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid,  
lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine,  
lactylic esters of fatty acids, stearyl-2-lactylate, stearyl lactylate, succinylated  
monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid  
30 esters of mono/diglycerides, cholate, taurocholate, glycocholate, deoxycholate,  
taurodeoxycholate, chenodeoxycholate, glycodeoxycholate, glycochenodeoxycholate,  
taurochenodeoxycholate, ursodeoxycholate, tauroursodeoxycholate,

1 glycooursodeoxycholate, cholylsarcosine, N-methyl taurocholate, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

5 Particularly preferred ionized ionizable surfactants are the ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, lysophosphatidylcholine, PEG-phosphatidylethanolamine, lactic esters of fatty acids, stearyl-2-lactylate, stearyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of  
10 mono/diglycerides, cholate, taurocholate, glycocholate, deoxycholate, taurodeoxycholate, glycodeoxycholate, cholylsarcosine, caproate, caprylate, caprate, laurate, oleate, lauryl sulfate, docusate, and salts and mixtures thereof, with the most preferred ionic surfactants being lecithin, lactic esters of fatty acids, stearyl-2-lactylate, stearyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides,  
15 citric acid esters of mono/diglycerides, taurocholate, caprylate, caprate, oleate, lauryl sulfate, docusate, and salts and mixtures thereof.

The absorption enhancing compositions include at least two surfactants, at least one of which is hydrophilic. In one embodiment, the present invention includes at two surfactants that are hydrophilic, and preferred hydrophilic surfactants are listed above. In  
20 another embodiment, the composition includes at least one hydrophilic surfactant and at least one hydrophobic surfactant.

In this embodiment, the hydrophobic surfactant can be an unionized ionizable surfactant. Preferably, the unionized ionizable surfactant is the unionized form of a surfactant selected from the group consisting of bile acids and analogues and derivatives thereof; lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof;  
25 carnitine fatty acid esters; alkylsulfates; fatty acids; acyl lactylates; mono-,diacetylated tartaric acid esters of mono-,diglycerides; succinylated monoglycerides; citric acid esters of mono-,diglycerides; and mixtures thereof.

More preferably, the un-ionized ionizable surfactant is the un-ionized form of a surfactant selected from the group consisting of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol,  
30

1 lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-  
phosphatidylethanolamine, lactic esters of fatty acids, stearyl-2-lactylate, stearyl  
lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of  
mono/diglycerides, citric acid esters of mono/diglycerides, cholic acid, taurocholic acid,  
5 glycocholic acid, deoxycholic acid, taurodeoxycholic acid, chenodeoxycholic acid,  
glycodeoxycholic acid, glycochenodeoxycholic acid, taurochenodeoxycholic acid,  
ursodeoxycholic acid, lithocholic acid, tauroursodeoxycholic acid, glyoursodeoxycholic  
acid, cholylsarcosine, N-methyl taurocholic acid, caproic acid, caprylic acid, capric acid,  
lauric acid, myristic acid, palmitic acid, oleic acid, ricinoleic acid, linoleic acid, linolenic  
10 acid, stearic acid, lauryl sulfate, tetraacetyl sulfate, lauroyl carnitine, palmitoyl carnitine,  
myristoyl carnitine, and mixtures thereof.

Still more preferably, the un-ionized ionizable surfactant is the un-ionized form of  
a surfactant selected from the group consisting of lecithin, lysolecithin,  
phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol,  
15 lysophosphatidylcholine, PEG-phosphatidylethanolamine, lactic esters of fatty acids,  
stearyl-2-lactylate, stearyl lactylate, succinylated monoglycerides, mono/diacetylated  
tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholic  
acid, taurocholic acid, glycocholic acid, deoxycholic acid, chenodeoxycholic acid,  
lithocholic acid, ursodeoxycholic acid, taurodeoxycholic acid, glycodeoxycholic acid,  
20 cholylsarcosine, caproic acid, caprylic acid, capric acid, lauric acid, oleic acid, lauryl  
sulfate, lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine, and mixtures thereof.

Most preferably, the un-ionized ionizable surfactant is the un-ionized form of a  
surfactant selected from the group consisting of lecithin, lactic esters of fatty acids,  
stearyl-2-lactylate, stearyl lactylate, succinylated monoglycerides, mono/diacetylated  
25 tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides,  
chenodeoxycholic acid, lithocholic acid, ursodeoxycholic acid, taurocholic acid, caprylic  
acid, capric acid, oleic acid, lauryl sulfate, docusate, lauroyl carnitine, palmitoyl carnitine,  
myristoyl carnitine, and mixtures thereof.

The hydrophobic surfactants can also be alcohols; polyoxyethylene alkylethers;  
30 fatty acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol  
fatty acids esters; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty  
acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid



1 derivatives of mono/diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters;  
polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block  
copolymers; transesterified vegetable oils; sterols; sterol derivatives; sugar esters; sugar  
ethers; sucroglycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated  
5 vegetable oils; and the un-ionized (neutral) forms of ionizable surfactants.

As with the hydrophilic surfactants, hydrophobic surfactants can be reaction mixtures of polyols and fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

10 Preferably, the hydrophobic surfactant is selected from the group consisting of fatty acids; lower alcohol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lactic acid derivatives of mono/diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyoxyethylene vegetable oils; polyoxyethylene  
15 hydrogenated vegetable oils; and reaction mixtures of polyols and fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

More preferred are lower alcohol fatty acids esters; polypropylene glycol fatty acid esters; propylene glycol fatty acid esters; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lactic acid derivatives of mono/diglycerides; sorbitan fatty acid esters;  
20 polyoxyethylene vegetable oils; and mixtures thereof, with glycerol fatty acid esters and acetylated glycerol fatty acid esters being most preferred. Among the glycerol fatty acid esters, the esters are preferably mono- or diglycerides, or mixtures of mono- and diglycerides, where the fatty acid moiety is a C<sub>6</sub> to C<sub>22</sub> fatty acid.

25 Also preferred are hydrophobic surfactants which are the reaction mixture of polyols and fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols. Preferred polyols are polyethylene glycol, sorbitol, propylene glycol, and pentaerythritol.

Specifically preferred hydrophobic surfactants include myristic acid; oleic acid; lauric acid; stearic acid; palmitic acid; PEG 1-4 stearate; PEG 2-4 oleate; PEG-4 dilaurate;  
30 PEG-4 dioleate; PEG-4 distearate; PEG-6 dioleate; PEG-6 distearate; PEG-8 dioleate; PEG 3-16 castor oil; PEG 5-10 hydrogenated castor oil; PEG 6-20 corn oil; PEG 6-20 almond oil; PEG-6 olive oil; PEG-6 peanut oil; PEG-6 palm kernel oil; PEG-6



1 hydrogenated palm kernel oil; PEG-4 capric/caprylic triglyceride, mono, di, tri, tetra esters  
of vegetable oil and sorbitol; pentaerythrityl di, tetra stearate, isostearate, oleate, caprylate,  
or caprate; polyglyceryl 2-4 oleate, stearate, or isostearate; polyglyceryl 4-10 pentaoleate;  
polyglyceryl-3 dioleate; polyglyceryl-6 dioleate; polyglyceryl-10 trioleate; polyglyceryl-3  
5 distearate; propylene glycol mono- or diesters of a C<sub>6</sub> to C<sub>20</sub> fatty acid; monoglycerides of  
C<sub>6</sub> to C<sub>20</sub> fatty acids; acetylated monoglycerides of C<sub>6</sub> to C<sub>20</sub> fatty acids; diglycerides of C<sub>6</sub>  
to C<sub>20</sub> fatty acids; lactic acid derivatives of monoglycerides; lactic acid derivatives of  
diglycerides; cholesterol; phytosterol; PEG 5-20 soya sterol; PEG-6 sorbitan tetra,  
hexastearate; PEG-6 sorbitan tetraoleate; sorbitan monolaurate; sorbitan monopalmitate;  
10 sorbitan mono, trioleate; sorbitan mono, tristearate; sorbitan monoisostearate; sorbitan  
sesquioleate; sorbitan sesquistearate; PEG 2-5 oleyl ether; POE 2-4 lauryl ether; PEG-2  
cetyl ether; PEG-2 stearyl ether; sucrose distearate; sucrose dipalmitate; ethyl oleate;  
isopropyl myristate; isopropyl palmitate; ethyl linoleate; isopropyl linoleate; and  
poloxamers.

15 Among the specifically preferred hydrophobic surfactants, most preferred are oleic  
acid; lauric acid; glyceryl monocaprate; glyceryl monocaprylate; glyceryl monolaurate;  
glyceryl monooleate; glyceryl dicaprate; glyceryl dicaprylate; glyceryl dilaurate; glyceryl  
dioleate; acetylated monoglycerides; propylene glycol oleate; propylene glycol laurate;  
polyglyceryl-3 oleate; polyglyceryl-6 dioleate; PEG-6 corn oil; PEG-20 corn oil; PEG-20  
20 almond oil; sorbitan monooleate; sorbitan monolaurate; POE-4 lauryl ether; POE-3 oleyl  
ether; ethyl oleate; and poloxamers.

## 2. Therapeutic Agents

The hydrophilic therapeutic agents suitable for use in the pharmaceutical systems  
and methods of the present invention are not particularly limited, as the absorption  
25 enhancing compositions are surprisingly capable of delivering a wide variety of  
hydrophilic therapeutic agents. Suitable hydrophilic therapeutic agents include  
hydrophilic drugs (*i.e.*, conventional non-peptidic drugs), hydrophilic macromolecules  
such as cytokines, peptidomimetics, peptides, proteins, toxoids, sera, antibodies, vaccines,  
nucleosides, nucleotides and genetic material, and other hydrophilic compounds, such as  
30 nucleic acids. The aqueous solubility of the hydrophilic therapeutic agent should be  
greater than about 1 mg/mL.

1       The hydrophilic therapeutic agent can be solubilized or suspended in a  
preconcentrate (before dilution with an aqueous diluent), added to the preconcentrate prior  
to dilution, added to the diluted preconcentrate, or added to an aqueous diluent prior to  
mixing with the preconcentrate. The hydrophilic therapeutic agent can also be co-  
5       administered as part of an independent dosage form, for therapeutic effect. Optionally, the  
hydrophilic therapeutic agent can be present in a first, solubilized amount, and a second,  
non-solubilized (suspended) amount. Such hydrophilic therapeutic agents can be any  
agents having therapeutic or other value when administered to an animal, particularly to a  
mammal, such as drugs, nutrients, cosmetics (cosmeceuticals), and diagnostic agents. It  
10       should be understood that while the invention is described with particular reference to its  
value for oral dosage forms, the invention is not so limited. Thus, hydrophilic drugs,  
nutrients, cosmetics and diagnostic agents which derive their therapeutic or other value  
from, for example, transmembrane (transport across a membrane barrier of therapeutic  
significance), nasal, buccal, rectal, vaginal or pulmonary administration, are still  
15       considered to be suitable for use in the present invention.

Specific non-limiting examples of therapeutic agents that can be used in the  
pharmaceutical compositions of the present invention include analgesics and anti-  
inflammatory agents, anthelmintics, anti-arrhythmic agents, anti-asthma agents, anti-  
bacterial agents, anti-viral agents, anti-coagulants, anti-depressants, anti-diabetics, anti-  
20       epileptics, anti-fungal agents, anti-gout agents, anti-hypertensive agents, anti-malarials,  
anti-migraine agents, anti-muscarinic agents, anti-neoplastic agents and  
immunosuppressants, anti-protozoal agents, anti-thyroid agents, anti-tussives, anxiolytic,  
sedatives, hypnotics and neuroleptics,  $\beta$ -Blockers, cardiac inotropic agents,  
corticosteroids, diuretics, anti-parkinsonian agents, gastro-intestinal agents, histamine H<sub>1</sub>-  
25       receptor antagonists, keratolytics, lipid regulating agents, muscle relaxants, anti-anginal  
agents, nutritional agents, analgesics, sex hormones, stimulants, cytokines,  
peptidomimetics, peptides, proteins, toxoids, sera, antibodies, vaccines, nucleosides,  
nucleotides and genetic material, and nucleic acids. Amphiphilic therapeutic agents are  
also included, provided they have a water solubility of greater than about 1 mg/mL.

30       In one embodiment, the hydrophilic therapeutic agent is a nutritional agent.

In another embodiment, the hydrophilic therapeutic agent is a cosmeceutical agent.

In another embodiment, the hydrophilic therapeutic agent is a diagnostic agent.

1           Although the invention is not limited thereby, examples of hydrophilic therapeutic agents suitable for use in the compositions and methods of the present invention include the following preferred compounds, as well as their pharmaceutically acceptable salts, isomers, esters, ethers and other derivatives:

5           acarbose; acyclovir; acetyl cysteine; acetylcholine chloride; alatrofloxacin; alendronate; alglucerase; amantadine hydrochloride; ambenonium; amifostine; amiloride hydrochloride; aminocaproic acid; amphotericin B; antihemophilic factor (human); antihemophilic factor (porcine); antihemophilic factor (recombinant); aprotinin; asparaginase; atenolol; atracurium besylate; atropine; azithromycin; aztreonam; BCG  
10 vaccine; bacitracin; becalermín; belladonna; bepridil hydrochloride; bleomycin sulfate; calcitonin human; calcitonin salmon; carboplatin; capecitabine; capreomycin sulfate; cefamandole nafate; cefazolin sodium; cefepime hydrochloride; cefixime; cefonicid sodium; cefoperazone; cefotetan disodium; cefotoxime; cefoxitin sodium; ceftizoxime; ceftriaxone; cefuroxime axetil; cephalixin; cephapirin sodium; cholera vaccine; chronic  
15 gonadotropin; cidofovir; cisplatin; cladribine; clidinium bromide; clindamycin and clindamycin derivatives; ciprofloxacin; clondronate; colistimethate sodium; colistin sulfate; cortocotropin; cosyntropin; cromalyn sodium; cytarabine; daltaperin sodium; danaproid; deforoxamine; denileukin diftitox; desmopressin; diatrizoate meglumine and diatrizoate sodium; dicyclomine; didanosine; dirithromycin; dopamine hydrochloride;  
20 dornase alpha; doxacurium chloride; doxorubicin; editronate disodium; elanaprilat; enkephalin; enoxacin; enoxaprin sodium; ephedrine; epinephrine; epoetin alpha; erythromycin; esmol hydrochloride; factor IX; famciclovir; fludarabine; fluoxetine; foscarnet sodium; ganciclovir; granulocyte colony stimulating factor; granulocyte-macrophage stimulating factor; growth hormones- recombinant human; growth  
25 hormone- bovine; gentamycin; glucagon; glycopyrolate; gonadotropin releasing hormone and synthetic analogs thereof; GnRH; gonadorelin; grepafloxacin; hemophilus B conjugate vaccine; Hepatitis A virus vaccine inactivated; Hepatitis B virus vaccine inactivated; heparin sodium; indinavir sulfate; influenza virus vaccine; interleukin-2; interleukin-3; insulin-human; insulin lispro; insulin procine; insulin NPH; insulin aspart; insulin  
30 glargine; insulin detemir; interferon alpha; interferon beta; ipratropium bromide; isofosfamide; japanese encephalitis virus vaccine; lamivudine; leucovorin calcium; leuprolide acetate; levofloxacin; lincomycin and lincomycin derivatives; lobucavir;

1 lomefloxacin; loracarbef; mannitol; measles virus vaccine; meningococcal vaccine;  
 menotropins; mephenzolate bromide; mesalmine; methanamine; methotrexate;  
 methscopolamine; metformin hydrochloride; metoprolol; mezocillin sodium; mivacurium  
 5 chloride; mumps viral vaccine; nedocromil sodium; neostigmine bromide; neostigmine  
 methyl sulfate; neutontin; norfloxacin; octreotide acetate; ofloxacin; olpadronate;  
 oxytocin; pamidronate disodium; pancuronium bromide; paroxetine; pefloxacin;  
 pentamidine isethionate; pentostatin; pentoxifylline; periciclovir; pentagastrin;  
 phentolamine mesylate; phenylalanine; physostigmine salicylate; plague vaccine;  
 piperacillin sodium; platelet derived growth factor-human; pneumococcal vaccine  
 10 polyvalent; poliovirus vaccine inactivated; poliovirus vaccine live (OPV); polymixin B  
 sulfate; pralidoxine chloride; pramlintide; pregabalin; propofenone; propenthaline  
 bromide; pyridostigmine bromide; rabies vaccine; residronate; ribavarin; rimantadine  
 hydrochloride; rotavirus vaccine; salmetrol xinafoate; sincalide; small pox vaccine;  
 solatol; somatostatin; sparfloxacin; spectinomycin; stavudine; streptokinase; streptozocin;  
 15 suxamethonium chloride; tacrine hydrochloride; terbutaline sulfate; thiopeta; ticarcillin;  
 tiludronate; timolol; tissue type plasminogen activator; TNFR:Fc; TNK-tPA; trandolapril;  
 trimetrexate gluconate; trospectinomycin; trovafloxacin; tubocurarine chloride; tumor  
 necrosis factor; typhoid vaccine live; urea; urokinase; vancomycin; valaciclovir; valsartan;  
 varicella virus vaccine live; vasopressin and vasopressin derivatives; vecoronium bromide;  
 20 vinblastin; vincristine; vinorelbine; vitamin B12 ; warfarin sodium; yellow fever vaccine;  
 zalcitabine; zanamavir; zolandronate; and zidovudine.

Among the listed hydrophilic therapeutic agents, more preferred therapeutic agents  
 are:

25 acarbose; acyclovir; atracurium besylate; alendronate; alglucerase; amantadine  
 hydrochloride; amphotericin B; antihemophilic factor (human); antihemophilic factor  
 (porcine); antihemophilic factor (recombinant; azithromycin; calcitonin human; calcitonin  
 salmon; capecitabine; cefazolin sodium; cefonicid sodium; cefoperazone; cefoxitin  
 sodium; ceftizoxime; ceftriaxone; cefuroxime axetil; cephalixin; chrionic gonadotropin;  
 30 cidofovir; cladribine ; clindamycin and clindamycin derivatives; corticotropin;  
 cosyntropin; cromalyn sodium; cytarabine; daltaperin sodium; danaproid; desmopressin;  
 didanosine; dirithromycin; editronate disodium; enoxaprin sodium; epoetin alpha; factor  
 IX; famciclovir; fludarabine; foscarnet sodium; ganciclovir; granulocyte colony

1 stimulating factor; granulocyte-macrophage stimulating factor; growth hormones-  
recombinant human; growth hormone- Bovine; gentamycin; glucagon; gonadotropin  
releasing hormone and synthetic analogs thereof; GnRH; gonadorelin; hemophilus B  
conjugate vaccine; Hepatitis A virus vaccine inactivated; Hepatitis B virus vaccine  
5 inactivated; heparin sodium; indinavir sulfate; influenza virus vaccine; interleukin-2;  
interleukin-3; insulin-human; insulin lispro; insulin procine; insulin NPH; insulin aspart;  
insulin glargine; insulin detemir; interferon alpha; interferon beta; ipratropium bromide;  
isofosfamide; lamivudine; leucovorin calcium; leuprolide acetate; lincomycin and  
lincomycin derivatives; metformin hydrochloride; nedocromil sodium; neostigmine  
10 bromide; neostigmine methyl sulfate; neutontin; octreotide acetate; olpadronate;  
pamidronate disodium; pancuronium bromide; pentamidine isethionate; pentagastrin;  
physostigmine salicylate; poliovirus vaccine live (OPV); pyridostigmine bromide;  
residronate; ribavarin; rimantadine hydrochloride; rotavirus vaccine; salmetrol xinafoate;  
somatostatin; spectinomycin; stavudine; streptokinase; ticarcillin; tiludronate; tissue type  
15 plasminogen activator; TNFR:Fc; TNK-tPA; trimetrexate gluconate; trospectinomycin;  
tumor necrosis factor; typhoid vaccine live; urokinase; vancomycin; valaciclovir;  
vasopressin and vasopressin derivatives; vinblastin; vincristine; vinorelbine; warfarin  
sodium; zalcitabine; zanamavir; and zidovudine.

The most preferred hydrophilic therapeutic agents are:

20 acarbose; alendronate; amantadine hydrochloride; azithromycin; calcitonin human;  
calcitonin salmon; ceftriaxone; cefuroxime axetil; chrionic gonadotropin; cromalyn  
sodium; daltaperin sodium; danaproid; desmopressin; didanosine; editronate disodium;  
enoxaprin sodium; epoetin alpha; factor IX; famciclovir; foscarnet sodium; ganciclovir;  
granulocyte colony stimulating factor; granulocyte-macrophage stimulating factor; growth  
25 hormones- recombinant human; growth hormone- Bovine; glucagon; gonadotropin  
releasing hormone and synthetic analogs thereof; GnRH; gonadorelin; heparin sodium;  
indinavir sulfate; influenza virus vaccine; interleukin-2; interleukin-3; insulin-human;  
insulin lispro; insulin procine interferon alpha; interferon beta; leuprolide acetate;  
metformin hydrochloride; nedocromil sodium; neostigmine bromide; neostigmine methyl  
30 sulfate; neutontin; octreotide acetate; olpadronate; pamidronate disodium; residronate;  
rimantadine hydrochloride; salmetrol xinafoate; somatostatin; stavudine; ticarcillin;  
tiludronate; tissue type plasminogen activator; TNFR:Fc; TNK-tPA; tumor necrosis



1 factor; typhoid vaccine live; vancomycin; valaciclovir; vasopressin and vasopressin derivatives; zalcitabine; zanamavir and zidovudine.

Of course, salts, metabolic precursors, derivatives and mixtures of therapeutic agents may also be used where desired.

5 **3. Solubilizers**

If desired, the pharmaceutical compositions of the present invention can optionally include additional compounds to enhance the solubility of the therapeutic agent or the triglyceride in the composition. Examples of such compounds, referred to as "solubilizers", include:

10 alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcitol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives;

15 ethers of polyethylene glycols having an average molecular weight of about 200 to about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofurol, available commercially from BASF under the trade name Tetraglycol) or methoxy PEG (Union Carbide);

20 amides, such as 2-pyrrolidone, 2-piperidone,  $\epsilon$ -caprolactam, N-alkylpyrrolidone, N-hydroxyalkylpyrrolidone, N-alkylpiperidone, N-alkylcaprolactam, dimethylacetamide, and polyvinylpyrrolidone;

25 esters, such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate,  $\epsilon$ -caprolactone and isomers thereof,  $\delta$ -valerolactone and isomers thereof,  $\beta$ -butyrolactone and isomers thereof;

30 and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide (Arlasolve DMI (ICI)), N-methyl pyrrolidones (Pharmasolve (ISP)), monooctanoin, diethylene glycol monoethyl ether (available from Gattefosse under the trade name Transcutol), and water.

Mixtures of solubilizers are also within the scope of the invention. Except as indicated, these compounds are readily available from standard commercial sources.



1 Preferred solubilizers include triacetin, triethylcitrate, ethyl oleate, ethyl caprylate,  
dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone,  
polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins,  
ethanol, polyethylene glycol 200-100, glycofurol, transcitol, propylene glycol, and  
5 dimethyl isosorbide. Particularly preferred solubilizers include sorbitol, glycerol, triacetin,  
ethyl alcohol, PEG-400, glycofurol and propylene glycol.

The amount of solubilizer that can be included in compositions of the present  
invention is not particularly limited. Of course, when such compositions are ultimately  
administered to a patient, the amount of a given solubilizer is limited to a bioacceptable  
10 amount, which is readily determined by one of skill in the art. In some circumstances, it  
may be advantageous to include amounts of solubilizers far in excess of bioacceptable  
amounts, for example, to maximize the concentration of therapeutic agent, with excess  
solubilizer removed prior to providing the composition to a patient using conventional  
techniques, such as distillation or evaporation. Thus, if present, the solubilizer can be in a  
15 concentration of 50%, 100%, 200%, or up to about 400% by weight, based on the weight  
of the carrier. If desired, very small amounts of solubilizers may also be used, such as  
25%, 10%, 5%, 1% or even less. Typically, the solubilizer will be present in an amount of  
about 1% to about 100%, more typically about 5% to about 25% by weight or about 10%  
to about 25% by weight.

#### 20 4. Concentrations

The components of the absorption enhancing compositions of the present invention  
are present in amounts such that upon dilution with an aqueous diluent, the carrier forms  
an aqueous dispersion having a small particle size. The hydrophilic and optional  
hydrophobic surfactants should be present in amounts sufficient to improve the absorption  
25 of the hydrophilic therapeutic agent. It is surprisingly found that relatively large amounts  
of the surfactants can be used while still maintaining a small particle size upon dilution.

Without wishing to be bound by theory, it is believed that the absorption enhancers  
present in the compositions are able to enhance absorption by one or more of the following  
factors: effective presentation of an absorption enhancer to the site of enhancement;  
30 modulation of facilitated/active transport; transcellular permeability enhancement through  
favorable membrane perturbations; inhibition of efflux related transporters; inhibition of  
luminal or cellular enzymatic inactivation; paracellular transport enhancement through

1 loosening of tight junctions; induction of specific transporters to facilitate transport;  
altered biological binding characteristics; reduced degradation of the hydrophilic  
therapeutic agent; induction of transient water channels; and/or increased partitioning of  
the hydrophilic therapeutic agent by association with the absorption enhancer. The  
5 functionality is believed to be due to a combination of small particle size, appropriate  
absorption enhancers in amounts chosen to provide small particle size upon dilution, and  
non-dependence upon lipolysis by avoiding the use of triglycerides. Preferably, diesters of  
propylene glycol are also avoided.

10 The presence of at least two surfactants, at least one of which is hydrophilic, is  
believed to be particularly advantageous to provide better presentation of the absorption  
enhancing components at the absorption site. For example, the presence of each  
surfactant is believed to assist the absorption enhancement functionality of the other  
surfactants by reducing the size of the particles containing the absorption enhancing  
surfactant to minimize aqueous boundary layer control, and/or by solubilizing water-  
15 immiscible absorption enhancing surfactants to increase the thermodynamic activity of the  
surfactant at the absorption site.

A preferred method of assessing the appropriate component concentrations is to  
quantitatively measure the size of the particles of which the dispersion is composed.  
These measurements can be performed on commercially available particle size analyzers,  
20 such as, for example, a Nicomp particle size analyzer available from Particle Size  
Systems, Inc., of Santa Barbara, CA. Using this measure, aqueous dispersions according  
to the present invention have average particle sizes much smaller than the wavelength of  
visible light, whereas dispersions containing relative amounts of the components outside  
the appropriate range have more complex particle size distributions, with much greater  
25 average particle sizes. It is desirable that the average particle size be less than about 200  
nm, preferably less than about 100, more preferably less than about 50 nm, still more  
preferably less than about 30 nm, and most preferably less than about 20 nm. It is also  
preferred that the particle size distribution be mono-modal. These particle sizes can be  
measured at dilution amounts of 10 to 250-fold or more, preferably about 100 to about  
30 250-fold, as is typical of the dilution expected in the gastrointestinal tract.

In a preferred embodiment, the components of the absorption enhancing  
compositions are present in amounts such that the aqueous dispersion formed upon

1 dilution with an aqueous medium has a small particle size and is also substantially  
optically clear. The composition in the preconcentrate form, *i.e.*, before dilution with an  
aqueous diluent, need not be clear, as it is the clarity upon dilution with an aqueous diluent  
that is preferred. The dilution can be *in vitro* or *in vivo*, and optical clarity should be  
5 assessed at dilutions of about 10 to 250-fold or more, preferably about 100 to 250-fold, as  
is encountered in the gastrointestinal environment. It should be appreciated that when the  
desired dosage form includes an amount of the hydrophilic therapeutic agent that is  
suspended, but not solubilized, in the composition, the appropriate concentrations of the  
other components are determined by the optical clarity of the diluted composition without  
10 the suspended therapeutic agent.

In this preferred embodiment, the relative amounts of the components are readily  
determined by observing the properties of the resultant dispersion; *i.e.*, when the relative  
amounts are within the preferred range, the resultant aqueous dispersion is optically clear.  
When the relative amounts are outside the preferred range, the resulting dispersion is  
15 visibly "cloudy", resembling a conventional emulsion or multiple-phase system. The  
optical clarity of the aqueous dispersion can be measured using standard quantitative  
techniques for turbidity assessment. One convenient procedure to measure turbidity is to  
measure the amount of light of a given wavelength transmitted by the solution, using, for  
example, a UV-visible spectrophotometer. Using this measure, optical clarity corresponds  
20 to high transmittance, since cloudier solutions will scatter more of the incident radiation,  
resulting in lower transmittance measurements. If this procedure is used, care should be  
taken to insure that the composition itself does not absorb light of the chosen wavelength,  
as any true absorbance necessarily reduces the amount of transmitted light and falsely  
increases the quantitative turbidity value. In the absence of chromophores at the chosen  
25 wavelength, suitable dispersions at a dilution of 100X should have an apparent absorbance  
of less than about 0.3, preferably less than about 0.2, and more preferably less than about  
0.1.

Other methods of characterizing optical clarity known in the art may also be used,  
and any or all of the available methods may be used to ensure that the resulting aqueous  
30 dispersions possess the preferred optical clarity.

In one embodiment, the hydrophilic therapeutic agent is formulated in the dosage  
form of the absorption enhancing composition, and is present in any amount up to the

1 maximum amount that can be solubilized in the composition. In another embodiment, the  
hydrophilic therapeutic agent is present in the dosage form of the absorption enhancing  
composition in a first amount which is solubilized, and a second amount that remains  
unsolubilized but dispersed. This may be desirable when, for example, a larger dose of the  
5 hydrophilic therapeutic agent is desired. Of course, in this embodiment, the optical clarity  
or particle size of the resultant aqueous dispersion is determined before the second non-  
solubilized amount of the hydrophilic therapeutic agent is added. In another embodiment,  
the hydrophilic therapeutic agent is present in a dosage form separate from the dosage  
form of the absorption enhancing composition, and the amount of hydrophilic therapeutic  
10 agent is any convenient amount that can be formulated in the separate dosage form, such  
as a therapeutically effective amount. This separate dosage form of the hydrophilic  
therapeutic agent can be a dosage form of the present invention, or any conventional  
dosage form, preferably triglyceride free, such as a commercial dosage form.

15 Other considerations well known to those skilled in the art will further inform the  
choice of specific proportions of the components. These considerations include the degree  
of bioacceptability of the compounds, and the desired dosage of hydrophilic therapeutic  
agent to be provided.

20 Keeping the considerations discussed above in mind, it is important that the  
composition include sufficient amounts of the absorption enhancing components to  
provide a therapeutically meaningful increase in the rate and/or extent of bioabsorption.  
Thus, in general the total amount of absorption enhancing components forming the carrier  
should be at least about 10% by weight, preferably at least about 20%, based on the total  
weight of the preconcentrate composition. As shown in the examples herein, the total  
amount of the absorption enhancing components can be far greater than 20%, and these  
25 compositions are also within the scope of the present invention.

30 It is preferred that when the absorption enhancing composition includes at least  
two surfactants selected from the group consisting of sodium lauryl sulfate, oleic acid,  
linoleic acid, monoolein, lecithin, lysolecithin, deoxycholate, taurodeoxycholate,  
glycochenodeoxycholate, polyoxyethylene X-lauryl ether, where X is from 9 to 20,  
sodium tauro-24,25-dihydrofusidate, polyoxyethylene ether, polyoxyethylene sorbitan  
esters, p-t-octylphenoxypolyoxyethylene, N-lauryl- $\beta$ -D-maltopyranoside, 1-  
dodecylazacycloheptane-2-azone, and phospholipids, each surfactant is present in an

1 amount of greater than 10% by weight, based on the total weight of the pharmaceutical system.

Alternatively, appropriate coating can be applied to the dosage form to enable sufficient concentration/amount of the absorption enhancing surfactant/therapeutic agent/inhibitor at the site of absorption.

## 5. Stability

### 5.1 Enzyme Inhibitors

When the hydrophilic therapeutic agent is subject to enzymatic degradation, the compositions can include an enzyme inhibiting agent as an absorption enhancing agent. Enzyme inhibiting agents are shown for example, in Bernskop-Schnurch, A., "The use of inhibitory agents to overcome enzymatic barrier to perorally administered therapeutic peptides and proteins", *J. Controlled Release* 52, 1-16 (1998), the disclosure of which is incorporated herein by reference.

Generally, inhibitory agents can be divided into the following classes:

15 Inhibitors that are not based on amino acids, such as P-aminobenzamidine, FK-448, camostat mesylate, sodium glycocholate;

Amino acids and modified amino acids, such as aminoboronic acid derivatives and n-acetylcysteine;

20 Peptides and modified peptides, such as bacitracin, phosphinic acid dipeptide derivatives, pepstatin, antipain, leupeptin, chymostatin, elastatin, bestatin, hosphoramindon, puromycin, cytochalasin potatocarboxy peptidase inhibitor, and amastatin;

25 Polypeptide protease inhibitors, such as aprotinin (bovine pancreatic trypsin inhibitor), Bowman-Birk inhibitor and soybean trypsin inhibitor, chicken egg white trypsin inhibitor, chicken ovoidinhibitor, and human pancreatic trypsin inhibitor;

Complexing agents, such as EDTA, EGTA, 1,10- phenanthroline and hydroxyquinoline; and

30 Mucoadhesive polymers and polymer-inhibitor conjugates, such as polyacrylate derivatives, chitosan, cellulotics, chitosan-EDTA, chitosan-EDTA-antipain, polyacrylic acid-bacitracin, carboxymethyl cellulose-pepstatin, polyacrylic acid-Bowman-Birk inhibitor.



1       The choice and levels of the enzyme inhibitor are based on toxicity, specificity of  
the proteases and the potency of the inhibition. Enteric coated compositions of the present  
invention protect hydrophilic therapeutic peptides or proteins in a restricted area of drug  
liberation and absorption, and reduce or even exclude extensive dilution effects. The  
5       inhibitor can be suspended or solubilized in the composition preconcentrate, or added to  
the aqueous diluent or as a beverage.

Without wishing to be bound by theory, it is believed that an inhibitor can function  
solely or in combination as:

10       a competitive inhibitor, by binding at the substrate binding site of the enzyme,  
thereby preventing the access to the substrate; examples of inhibitors believed to operate  
by this mechanism are antipain, elastatinal and the Bowman Birk inhibitor;

      a non-competitive inhibitor which can be simultaneously bound to the enzyme site  
along with the substrate, as their binding sites are not identical; and/or

15       a complexing agent due to loss in enzymatic activity caused by deprivation of  
essential metal ions out of the enzyme structure.

#### 5.2     Water-Free Preconcentrates

      In a particular embodiment, the preconcentrate absorption enhancing composition--  
*i.e.*, the composition before dispersion in an aqueous medium-- is free of water. Water-  
free compositions are preferred to increase the physical and/or chemical stability of the  
20       composition or of individual components thereof, allowing for longer storage. In addition,  
water-free compositions offer advantages in processing, such as, for example, ease in  
encapsulation.

#### 6.     Other Additives

25       Other additives conventionally used in pharmaceutical compositions can be  
included, and these additives are well known in the art. Such additives include  
detackifiers, anti-foaming agents, buffering agents, antioxidants, preservatives, chelating  
agents, viscomodulators, tonicifiers, flavorants, colorants odorants, opacifiers, suspending  
agents, binders, fillers, plasticizers, lubricants, and mixtures thereof. The amounts of such  
additives can be readily determined by one skilled in the art, according to the particular  
30       properties desired.

      An acid or a base may be added to the composition to facilitate processing, or to  
prevent degradation of the hydrophilic therapeutic agent. Examples of pharmaceutically



1 acceptable bases include amino acids, amino acid esters, ammonium hydroxide, potassium  
hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium  
carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum  
silicate, synthetic hydrotalcite, magnesium aluminum hydroxide, diisopropylethylamine,  
5 ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, and  
the like. Also suitable are bases which are salts of a pharmaceutically acceptable acid,  
such as acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids,  
ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids,  
formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic  
10 acid, maleic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-  
toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid,  
thioglycolic acid, toluenesulfonic acid, uric acid, and the like. Salts of polyprotic acids,  
such as sodium phosphate, disodium hydrogen phosphate, and sodium dihydrogen  
phosphate can also be used. When the base is a salt, the cation can be any convenient and  
15 pharmaceutically acceptable cation, such as ammonium, alkali metals, alkaline earth  
metals, and the like. Preferred cations include sodium, potassium, lithium, magnesium,  
calcium and ammonium.

Suitable acids are pharmaceutically acceptable organic or inorganic acids.  
Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid,  
20 hydriodic acid, sulfuric acid, nitric acid, boric acid, phosphoric acid, and the like.  
Examples of suitable organic acids include acetic acid, acrylic acid, adipic acid, alginic  
acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric  
acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid,  
hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid,  
25 oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid,  
salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid,  
toluenesulfonic acid, uric acid and the like.

Although a wide variety of absorption enhancing components, solubilizers and  
additives can be used in the pharmaceutical systems of the present invention, in one  
30 embodiment, it is preferred that the composition be water-free in the preconcentrate form.  
In another embodiment, it is preferred that the composition be free of propylene glycol  
diesters. In another embodiment, it is preferred that the composition be free of cholesterol.

1 Of course, combinations of these preferred embodiments are also within the scope of the invention, so that the composition may, for example, be free of several or all of water, propylene glycol diesters and cholesterol.

## 7. Dosage Forms

5 The pharmaceutical compositions of the present invention can be formulated as a preconcentrate in a liquid, semi-solid, or solid form, or as an aqueous or organic diluted preconcentrate. In the diluted form, the diluent can be water, an aqueous solution, a buffer, an organic solvent, a beverage, a juice, or mixtures thereof. If desired, the diluent can include components soluble therein, such as a hydrophilic therapeutic agent, an  
10 enzyme inhibitor, solubilizers, additives, and the like.

The compositions can be processed according to conventional processes known to those skilled in the art, such as lyophilization, encapsulation, compression, melting, extrusion, balling, drying, chilling, molding, spraying, spray congealing, coating, comminution, mixing, homogenization, sonication, cryopelletization, spheronization, and  
15 granulation, to produce the desired dosage form.

The dosage form is not particularly limited. Thus, compositions of the present invention can be formulated as pills, capsules, caplets, tablets, granules, pellets, beads or powders. Granules, pellets, beads and powders can, of course, be further processed to form pills, capsules, caplets or tablets.

20 The dosage form can be designed for immediate release, controlled release, extended release, delayed release or targeted delayed release. The definitions of these terms are known to those skilled in the art. Furthermore, the dosage form release profile can be effected by a polymeric matrix composition, a coated matrix composition, a multiparticulate composition, a coated multiparticulate composition, an ion-exchange  
25 resin-based composition, an osmosis-based composition, or a biodegradable polymeric composition. Without wishing to be bound by theory, it is believed that the release may be effected through favorable diffusion, dissolution, erosion, ion-exchange, osmosis or combinations thereof.

30 When formulated as a capsule, the capsule can be a hard or soft gelatin capsule, a starch capsule, or a cellulosic capsule. Such dosage forms can further be coated with, for example, a seal coating, an enteric coating, an extended release coating, or a targeted delayed release coating.

1       The term "extended release coating" as used herein means a coating designed to  
effect the delivery of a hydrophilic therapeutic agent, an enzyme inhibitor, or the carrier,  
over an extended period of time. Preferably, the extended release coating is a pH-  
independent coating formed of, for example, ethyl cellulose, hydroxypropyl cellulose,  
5 methylcellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, acrylic esters, or  
sodium carboxymethyl cellulose. Various extended release dosage forms can be readily  
designed by one skilled in art to achieve delivery of a hydrophilic therapeutic agent, an  
absorption enhancing carrier or an enzyme inhibitor to both the small and large intestines,  
to only the small intestine, or to only the large intestine, depending upon the choice of  
10 coating materials and/or coating thickness.

Dosage forms of the compositions of the present invention can also be formulated  
as enteric coated delayed release oral dosage forms, *i.e.*, as an oral dosage form of a  
pharmaceutical composition as described herein which utilizes an enteric coating to effect  
release of a hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing  
15 carrier in the lower gastrointestinal tract. The enteric coated dosage form may be a  
compressed or molded or extruded tablet/mold (coated or uncoated) containing granules,  
pellets, beads or particles of the hydrophilic therapeutic agent, enzyme inhibitor and/or  
absorption enhancing carrier, which are themselves coated or uncoated. The enteric coated  
oral dosage form may also be a capsule (coated or uncoated) containing pellets, beads or  
20 granules of the hydrophilic therapeutic agent, enzyme inhibitor and/or absorption  
enhancing carrier which are themselves coated or uncoated.

The term "enteric coating" as used herein relates to a mixture of pharmaceutically  
acceptable excipients which is applied to, combined with, mixed with or otherwise added  
to the hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing carrier.  
25 The coating may be applied to a compressed or molded or extruded tablet, a gelatin  
capsule, and/or pellets, beads, granules or particles of the hydrophilic therapeutic agent,  
enzyme inhibitor and/or absorption enhancing carrier. The coating may be applied through  
an aqueous dispersion or after dissolving in appropriate solvent. Additional additives and  
their levels, and selection of a primary coating material or materials will depend on the  
30 following properties:

1. resistance to dissolution and disintegration in the stomach;

- 1           2.     impermeability to gastric fluids and drug/carrier/enzyme while in the stomach;
3.     ability to dissolve or disintegrate rapidly at the target intestine site;
4.     physical and chemical stability during storage;
- 5           5.     non-toxicity;
6.     easy application as a coating (substrate friendly); and
7.     economical practicality.

10           The term "delayed release" as used herein refers to the delivery of the hydrophilic therapeutic agent, an enzyme inhibitor, and/or the absorption enhancing carrier, which is effected by formulating the composition so that the release can be accomplished at some generally predictable location in the lower intestinal tract more distal to that which would have been accomplished if there had been no delayed release alterations. The preferred method for delay of release is coating. Coating prevents exposure of the hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing carrier to the epithelial and mucosal tissue of the buccal cavity, pharynx, esophagus, and stomach, and to the enzymes associated with these tissues. This helps to protect the hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing carrier and the tissues from any adverse event prior to the delivery at the desired site of absorption. Furthermore, coated compositions of the present invention allow balancing enhancement effectiveness, active protection, and safety liability through coating controlled dilution of the hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing carrier upon administration through delayed release or sustained release. Multiple enteric coatings targeted to release hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing carrier at various regions in the lower gastrointestinal tract would enable even more effective and sustained improved delivery throughout the lower gastrointestinal tract.

25           Any coatings should be applied to a sufficient thickness such that the entire coating does not dissolve in the gastrointestinal fluids at pH below about 5, but does dissolve at pH about 5 and above. It is expected that any anionic polymer exhibiting a pH-dependent solubility profile can be used as an enteric coating in the practice of the present invention to achieve delivery of the hydrophilic therapeutic agent, enzyme inhibitor and/or absorption enhancing carrier to the lower gastrointestinal tract. The coating chosen should

1 be compatible with the hydrophilic therapeutic agent and the other selected components. The preferred polymers for use in the present invention are anionic carboxylic polymers. The more preferred polymers and compatible mixtures thereof, and some of their properties, include, but are not limited to:

5 Shellac, also called purified lac, a refined product obtained from the resinous secretion of an insect. This coating dissolves in media of pH >7.

Acrylic polymers (preferred). The performance of acrylic polymers (primarily their solubility in biological fluids) can vary based on the degree and type of substitution. Examples of suitable acrylic polymers include methacrylic acid copolymers and ammonio methacrylate copolymers. The Eudragit series E, L, S, RL, RS and NE (Rohm Pharma) are available as solubilized in organic solvent, aqueous dispersion, or dry powders. The Eudragit series RL, NE, and RS are insoluble in the gastrointestinal tract but are permeable and are used primarily for extended release. The Eudragit series E dissolve in the stomach. The Eudragit series L, L-30D and S are insoluble in stomach and dissolve in the intestine.

Cellulose Derivatives (also preferred). Examples of suitable cellulose derivatives are:

ethyl cellulose;

20 reaction mixtures of partial acetate esters of cellulose with phthalic anhydride. The performance can vary based on the degree and type of substitution. Cellulose acetate phthalate (CAP) dissolves in pH > 6. Aquateric (FMC) is an aqueous based system and is a spray dried CAP pseudolatex with particles < 1µm. Other components in Aquateric can include pluronics, Tweens, and acetylated monoglycerides;

25 cellulose acetate trimellitate (Eastman);

methylcellulose (Pharmacoat, Methocel);

hydroxypropyl methyl cellulose phthalate (HPMCP). The performance can vary based on the degree and type of substitution. HP-50, HP-55, HP-55S, HP-55F grades are suitable;

30 hydroxypropyl methyl cellulose succinate (HPMCS; AQOAT (Shin Etsu)).

The performance can vary based on the degree and type of substitution. Suitable grades include AS-LG (LF), which dissolves at pH 5, AS-MG (MF), which dissolves at



1 pH 5.5, and AS-HG (HF), which dissolves at higher pH. These polymers are offered as granules, or as fine powders for aqueous dispersions;

Poly Vinyl Acetate Phthalate (PVAP). PVAP dissolves in pH >5, and it is much less permeable to water vapor and gastric fluids; and

5 Cotteric (by Colorcon).

Combinations of the above materials can also be used.

The coating can, and usually does, contain a plasticizer and possibly other coating excipients such as colorants, talc, and/or magnesium stearate, which are well known in the art. Suitable plasticizers include: triethyl citrate (Citroflex 2), triacetin (glyceryl triacetate), acetyl triethyl citrate (Citroflex A2), Carbowax 400 (polyethylene glycol 400),  
10 diethyl phthalate, tributyl citrate, acetylated monoglycerides, glycerol, fatty acid esters, propylene glycol, and dibutyl phthalate. In particular, anionic carboxylic acrylic polymers usually will contain 10-25% by weight of a plasticizer, especially dibutyl phthalate, polyethylene glycol, triethyl citrate and triacetin. Conventional coating techniques such as  
15 spray or pan coating are employed to apply coatings. The coating thickness must be sufficient to ensure that the oral dosage form remains intact until the desired site of topical delivery in the lower intestinal tract is reached.

Colorants, detackifiers, surfactants, antifoaming agents, lubricants, stabilizers such as hydroxy propyl cellulose, acid/base may be added to the coatings besides plasticizers to  
20 solubilize or disperse the coating material, and to improve coating performance and the coated product.

A particularly suitable methacrylic copolymer is Eudragit L.RTM, particularly L-30D.RTM and Eudragit 100-55.RTM, manufactured by Rohm Pharma, Germany. In Eudragit L-30 D.RTM, the ratio of free carboxyl groups to ester groups is approximately  
25 1:1. Further, the copolymer is known to be insoluble in gastrointestinal fluids having pH below 5.5, generally 1.5-5.5, *i.e.*, the pH generally present in the fluid of the upper gastrointestinal tract, but readily soluble or partially soluble at pH above 5.5, *i.e.*, the pH generally present in the fluid of lower gastrointestinal tract.

Another methacrylic acid polymer which is suitable for use in coating the oral  
30 dosage forms and/or the granules, particles, pellets or beads of absorption enhancing carrier and/or hydrophilic therapeutic agent which can be employed in the compositions and methods described herein, either alone or in combination with other coatings, is



1 Eudragit S.RTM, manufactured by Rohm Pharma, Germany. Eudragit S.RTM. differs  
from Eudragit L-30-D.RTM only insofar as the ratio of free carboxyl groups to ester  
groups is approximately 1:2. Eudragit S.RTM is insoluble at pH below 5.5, but unlike  
Eudragit L-30-D.RTM, is poorly soluble in gastrointestinal fluids having pH of 5.5-7.0,  
5 such as is present in the small intestine media. This copolymer is soluble at pH 7.0 and  
above, *i.e.*, the pH generally found in the colon. Eudragit S.RTM can be used alone as a  
coating to provide delivery of the hydrophilic therapeutic agent and/or the absorption  
enhancing carrier beginning at the large intestine via a delayed release mechanism. In  
addition, Eudragit S.RTM, being poorly soluble in intestinal fluids below pH 7, can be  
10 used in combination with Eudragit L-30-D.RTM, soluble in intestinal fluids above pH 5.5,  
in order to effect a delayed release composition which can be formulated to deliver the  
hydrophilic therapeutic agent and/or absorption enhancing carrier to various segments of  
the intestinal tract. The more Eudragit L-30 D.RTM used the more proximal release and  
delivery begins, and the more Eudragit S.RTM used, the more distal release and delivery  
15 begins. Both Eudragit L-30-D-RTM and Eudragit S.RTM can be substituted with other  
pharmaceutically acceptable polymers with similar pH solubility characteristics.

Preferred materials include shellac, acrylic polymers, cellulosic derivatives,  
polyvinyl acetate phthalate, and mixtures thereof. More preferred materials include  
Eudragit series E, L, S, RL, RS, NE, L.RTM, L300.RTM, S.RTM, 100-55RTM, cellulose  
20 acetate phthalate, Aquateric, cellulose acetate trimellitate, ethyl cellulose, hydroxypropyl  
methyl cellulose phthalate, hydroxypropyl methyl cellulose succinate, poly vinyl acetate  
phthalate, and Cotteric. Most preferred materials include Eudragit series L.RTM,  
L300.RTM, S.RTM, L100-55RTM, cellulose acetate phthalate, Aquateric, ethyl cellulose,  
hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose succinate, poly  
25 vinyl acetate phthalate, and Cotteric.

Extended release and targeted delayed release coatings for dosage forms of the  
compositions of the present invention are described more completely in U.S. Patent Nos.  
5,622,721 and 5,686,105, the disclosures of which are incorporated herein by reference in  
their entirety.

30 Although formulations specifically suited to oral administration are presently  
preferred, the compositions of the present invention can also be formulated for topical,  
transdermal, buccal, nasal, ocular, pulmonary, vaginal, rectal, transmucosal or parenteral

1 administration, as well as for oral administration. Thus, the dosage form can be a solution, suspension, emulsion, cream, ointment, lotion, suppository, spray, aerosol, paste, gel, drops, douche, ovule, wafer, troche, cachet, syrup, elixer, or other dosage form, as desired. If formulated as a suspension, the composition can further be processed in capsule form.

5 When formulated as a sprayable solution or dispersion, a dosage form of a multiparticulate carrier coated onto a substrate with the pharmaceutical compositions described herein can be used. The substrate can be a granule, a particle, a pellet or a bead, for example, and formed of a therapeutic agent or a pharmaceutically acceptable material. The multiparticulate carrier can be enteric coated with a pharmaceutically acceptable  
10 material, such as the targeted delayed enteric coatings and extended release coatings of U.S. Patent Nos. 5,622,721 and 5,686,105, described above. The multiparticulate carrier, coated or uncoated, can further be processed by encapsulation, and the resultant capsule can also be coated, if desired.

Other additives may be included, such as are well-known in the art, to impart the  
15 desired consistency and other properties to the formulation.

#### 8. Specific Embodiments

In all of the embodiments described herein, the components of the absorption enhancing carrier are present in amounts such that upon mixing with an aqueous diluent, either *in vitro* or *in vivo*, the carrier forms an aqueous dispersion having a small average  
20 particle size. In a preferred embodiment, the dispersion is also substantially optically clear. In these preferred embodiments, the optical clarity or particle size in an aqueous dispersion defines the preferred relative concentrations of the components as described above, but does not restrict the dosage form of the compositions to an aqueous dispersion, nor does it limit the compositions of the invention to optically clear dosage forms. Thus,  
25 the preferred concentrations of the components are determined by the particle size and/or optical clarity of a dispersion formed by the composition preconcentrate and an aqueous diluent in a dilution of about 10 to about 250-fold, as a preliminary matter. Once the appropriate concentrations are determined, the pharmaceutical compositions can be formulated as described in the preceding section, without regard to the optical clarity of  
30 the ultimate formulation in these preferred embodiments.

In one particular embodiment, the present invention provides a triglyceride-free pharmaceutical system including an absorption enhancing composition including at least

1 two surfactants, at least one of which is hydrophilic. The surfactants are present in  
amounts such that the carrier forms an aqueous dispersion having a small average particle  
size. In one preferred aspect of this embodiment, the average particle size is less than  
about 200 nm upon mixing with an aqueous diluent. In another preferred aspect of this  
5 embodiment, the aqueous dispersion is substantially optically clear. Preferably, the  
composition includes a mixture of hydrophilic and hydrophobic surfactants.

The pharmaceutical system also includes a hydrophilic therapeutic agent. The  
hydrophilic therapeutic agent can be solubilized, suspended, or partially solubilized and  
suspended, in the dosage form of the absorption enhancing composition. Alternatively,  
10 the hydrophilic therapeutic agent can be provided in a separate dosage form, so that in use,  
the dosage form of the absorption-enhancing composition and the dosage form of the  
hydrophilic therapeutic agent are co-administered. In the latter aspect, the pharmaceutical  
system can make use of any dosage form of a hydrophilic therapeutic agent, such as  
commercially available dosage forms. The pharmaceutical system is particularly  
15 advantageous, since the absorption enhancing pharmaceutical composition improves the  
functionality of even conventionally formulated hydrophilic therapeutic agents.  
Preferably, the dosage form of the absorption enhancing pharmaceutical composition, with  
or without a hydrophilic therapeutic agent, is an orally administrable dosage form. If the  
hydrophilic therapeutic agent is provided in a separate dosage form, it is preferred that the  
20 dosage form of the hydrophilic therapeutic agent also be an orally administrable dosage  
form.

In another aspect, the present invention provides a method of improving the  
bioabsorption of a hydrophilic therapeutic agent administered to a patient, such as an  
animal, preferably a mammal, and more preferably a human. The method includes the  
25 steps of providing a dosage form of an absorption enhancing composition, providing a  
hydrophilic therapeutic agent, and administering the dosage form of the absorption  
enhancing composition and the hydrophilic therapeutic agent to the patient. The dosage  
form of the absorption enhancing composition can be any of the dosage forms described  
above. Similarly, the hydrophilic therapeutic agent can be provided solubilized,  
30 suspended, or partially solubilized and suspended, in the dosage form of the absorption  
enhancing composition, or can be provided in a separate dosage form. It is surprisingly  
found that by administering a hydrophilic therapeutic agent contained within, or co-

1 administered with, a dosage form of an absorption enhancing composition of the present  
invention, the rate and/or extent, or the consistency in the rate and/or extent of  
bioabsorption of the hydrophilic therapeutic agent is unexpectedly enhanced. Thus, in one  
5 method increases the rate and/or extent of bioabsorption. In another aspect, the  
method increases the consistency of the rate and/or extent of bioabsorption. In this latter  
aspect, the rate and/or extent of bioabsorption can be greater than or less than the rate that  
would be seen using conventional methods.

In other embodiments, the absorption enhancing compositions in the  
pharmaceutical systems and methods of the present invention can be free of water in the  
10 preconcentrate form, free of propylene glycol diesters, and/or free of cholesterol. All of  
the compositions, however, are substantially free of triglycerides.

#### 9. Preparation of Pharmaceutical Compositions

The pharmaceutical compositions of the present invention can be prepared by  
conventional methods well known to those skilled in the art. Of course, the specific  
15 method of preparation will depend upon the ultimate dosage form. For dosage forms  
substantially free of water, *i.e.*, when the composition is provided in a pre-concentrate  
form for later dispersion *in vitro* or *in vivo* in an aqueous system, the composition is  
prepared by simple mixing of the components to form a pre-concentrate. The mixing  
process can be aided by gentle heating, if desired. For compositions in the form of an  
20 aqueous dispersion, the pre-concentrate form is prepared, then the appropriate amount of  
an aqueous diluent is added. Upon gentle mixing, an aqueous dispersion is formed. If any  
water-soluble enzyme inhibitors or additives are included, these may be added first as part  
of the pre-concentrate, or added later to the aqueous dispersion, as desired. The dosage  
forms of the absorption enhancing compositions can be prepared with or without a  
25 hydrophilic therapeutic agent, and a hydrophilic therapeutic agent may also be provided in  
the diluent, if desired, or in a separate dosage form.

As previously noted, in another embodiment, the present invention includes a  
multi-phase dispersion containing a hydrophilic therapeutic agent. In this embodiment, a  
dosage form includes a hydrophilic therapeutic agent and an absorption enhancing  
30 composition which forms an aqueous dispersion upon mixing with an aqueous diluent, and  
an additional amount of non-solubilized hydrophilic therapeutic agent. Thus, the term  
"multi-phase" as used herein to describe these compositions of the present invention

1 means a composition which when mixed with an aqueous diluent forms an aqueous phase  
and a particulate dispersion phase. The composition components are as described above,  
and can include any of the surfactants, therapeutic agents, solubilizers and additives  
previously described. An additional amount of hydrophilic therapeutic agent is included  
5 in the composition. This additional amount is not solubilized in the composition, and  
upon mixing with an aqueous system is present as a separate dispersion phase. The  
additional amount is optionally a milled, micronized, or precipitated form. Thus, upon  
dilution, the composition contains two phases: an aqueous dispersion phase containing a  
first, solubilized amount of the hydrophilic therapeutic agent, and a second, non-  
10 solubilized amount of the hydrophilic therapeutic agent dispersed therein.

One skilled in the art will appreciate that a hydrophilic therapeutic agent may have  
a greater solubility in the pre-concentrate composition than in the aqueous dispersion, so  
that meta-stable, supersaturated solutions having apparent optical clarity but containing a  
hydrophilic therapeutic agent in an amount in excess of its solubility in the aqueous  
15 dispersion can be formed. Such super-saturated solutions, whether characterized as  
aqueous dispersions (as initially formed) or as multi-phase solutions (as would be  
expected if the meta-stable state breaks down), are also within the scope of the present  
invention.

The multi-phase formulation can be prepared by the methods described above. A  
20 pre-concentrate is prepared by simple mixing of the components, with the aid of gentle  
heating, if desired. It is convenient to consider the hydrophilic therapeutic agent as  
divided into two portions, a first solubilizable portion which will be solubilized and  
contained within the clear aqueous dispersion upon dilution, and a second non-  
solubilizable portion which will remain non-solubilized. When the ultimate dosage form  
25 is non-aqueous, the first and second portions of the hydrophilic therapeutic agent are both  
included in the pre-concentrate mixture. When the ultimate dosage form is aqueous, the  
composition can be prepared in the same manner, and upon dilution in an aqueous system,  
the composition will form the two phases as described above, with the second non-  
solubilizable portion of the hydrophilic therapeutic agent dispersed or suspended in the  
30 aqueous system, and the first solubilizable portion of the hydrophilic therapeutic agent  
solubilized in the composition. Alternatively, when the ultimate dosage form is aqueous,  
the pre-concentrate can be prepared including only the first, solubilizable portion of the



1 hydrophilic therapeutic agent. This pre-concentrate can then be diluted in an aqueous system to form an aqueous dispersion, to which is then added the second, non-solubilizable portion of the hydrophilic therapeutic agent to form a multi-phase aqueous composition.

5 **B. Characteristics of the Pharmaceutical Compositions and Methods**

The dispersions formed upon dilution of the pharmaceutical compositions of the present invention are believed to have some or all of the following characteristics:

10 Rapid formation: upon dilution with an aqueous diluent, the composition forms an aqueous dispersion of small particle size very rapidly; *i.e.*, the dispersion appears to form instantaneously.

15 Optical clarity: in a preferred embodiment, the dispersions are essentially optically clear to the naked eye, and show no readily observable signs of heterogeneity, such as turbidity or cloudiness. More quantitatively, dispersions of the pharmaceutical compositions of the present invention have absorbances (400 nm) of less than about 0.3, and generally less than about 0.1, at 100X dilution in this preferred embodiment. In the multi-phase embodiment of the compositions described herein, it should be appreciated that the optical clarity of the aqueous phase will be obscured by the dispersed particulate non-solubilized hydrophilic therapeutic agent.

20 Small Particle Size: dispersions of the pharmaceutical compositions of the present invention contain particles of very small size. Preferably, the average size is less than about 200 nm, more preferably less than about 100 nm, still more preferably less than about 50 nm and most preferably less than about 20 nm. The small particle size promotes efficient transport of the absorption enhancing components to the absorption site.

25 Robustness to dilution: the dispersions are surprisingly stable to dilution in aqueous solution. The absorption enhancing composition remains solubilized for at least the period of time relevant for absorption.

The unique pharmaceutical compositions and methods of the present invention present a number of significant and unexpected advantages, including:

30 Efficient transport: The particle sizes in the aqueous dispersions of the present invention are much smaller than the larger particles characteristic of vesicular, emulsion or microemulsion phases. This reduced particle size enables more efficient transport through the intestinal aqueous boundary layer, and through the absorptive brush border membrane.



1 More efficient transport to absorptive sites leads to improved and more consistent  
absorption of therapeutic agents. Moreover, the present invention allows absorption  
enhancing components to be delivered to the absorption site along with the hydrophilic  
therapeutic agent, to further enhance absorption.

5 No dependence on lipolysis: The lack of triglycerides provides pharmaceutical  
compositions that are not dependent upon lipolysis, and upon the many poorly  
characterized factors which affect the rate and extent of lipolysis, for effective presentation  
of a therapeutic agent to an absorptive site. Such factors include the presence of  
composition components which may inhibit lipolysis; patient conditions which limit  
10 production of lipase, such as pancreatic lipase secretory diseases; and dependence of  
lipolysis on stomach pH, endogenous calcium concentration, and presence of co-lipase or  
other digestion enzymes. The lack of lipolysis dependence further provides transport  
which is less prone to suffer from any lag time between administration and absorption  
caused by the lipolysis process, enabling a more rapid onset of therapeutic action and  
15 better bioperformance characteristics. In addition, pharmaceutical compositions of the  
present invention can make use of hydrophilic surfactants which might otherwise be  
avoided or limited due to their potential lipolysis inhibiting effects.

Non-dependence on bile and meal fat contents: Due to the higher solubilization  
potential over bile salt micelles, the present compositions are less dependent on  
20 endogenous bile and bile related patient disease states, and meal fat contents. These  
advantages overcome meal-dependent absorption problems caused by poor patient  
compliance with meal-dosage restrictions.

Faster dissolution and release: Due to the robustness of compositions of the  
present invention to dilution, the components of the absorption enhancing composition  
25 remain solubilized and thus do not suffer problems of precipitation or agglomeration in the  
time frame relevant for absorption. In addition, the therapeutic agent is presented in small  
particle carriers, and is not limited in dilution rate by entrapment in emulsion carriers.

Consistent performance: Aqueous dispersions of the present invention are  
thermodynamically stable for the time period relevant for absorption, and can be more  
30 predictably reproduced, thereby limiting variability in bioavailability-- a particularly  
important advantage for therapeutic agents with a narrow therapeutic index.

1        Less prone to gastric emptying delays: Unlike conventional triglyceride-containing formulations, the present compositions are less prone to gastric emptying delays, resulting in faster absorption. Further, the particles in dispersions of the present invention are less prone to unwanted retention in the gastro-intestinal tract.

5        Better targeted absorption: The compositions of the present invention can be targeted to specific absorption sites through targeted enteric coating or extended release coating, thus minimizing dilution effects and optimizing activity of the hydrophilic therapeutic agent.

10       These and other advantages of the present invention, as well as aspects of preferred embodiments, are illustrated more fully in the Examples which follow.

### EXAMPLES

#### Example 1: Preparation of Compositions

15       A simple pre-concentrate is prepared as follows. Predetermined weighed amounts of the components are stirred together to form a homogeneous mixture. For combinations that are poorly miscible, the mixture can be gently heated to aid in formation of the homogeneous mixture. If the composition is to include a hydrophilic therapeutic agent, the chosen hydrophilic therapeutic agent in a predetermined amount can be added and stirred until solubilized. Optionally, solubilizers or additives are included by simple mixing.

20       To form an aqueous dispersion of the pre-concentrate, a predetermined amount of an aqueous medium such as purified water, buffer solution, or aqueous simulated physiological solution, is added to the pre-concentrate, and the resultant mixture is stirred to form an aqueous dispersion. Of course, when the dosage form is an aqueous dispersion, any of the components that are readily water-soluble, including the hydrophilic therapeutic agent, can be provided in the diluent solution.

#### Examples 2-3: Membrane Transport and In Situ Absorption Studies

30       Compositions of the present invention were tested by two different methods, to demonstrate the improved delivery of hydrophilic therapeutic agents incorporated within or co-administered with compositions including an absorption enhancing carrier. In one set of studies, the relative permeability of membranes to hydrophilic therapeutic agents was compared with and without the presence of an absorption enhancing carrier ("Membrane Transport Study"). In a second set of studies, the relative absorption of a

hydrophilic therapeutic agent in rat mesenteric veins was compared with and without the presence of an absorption enhancing carrier ("Relative Absorption Study").

For Examples 2 and 3, the following compositions were used, as described in the following sections. For each sample composition, absorbance measurements were made at 400 nm, using a UV-Visible spectrophotometer, at a dilution of 25X with distilled water. In addition, particle size measurements were made using a particle size analyzer, and the volume-weighted average particle sizes are shown along with sample characteristics in Table 19. The standard deviation of the particle size distribution is shown in parentheses next to the average particle size.

Table 19: Sample Compositions and Characterizations

Sample No.	Components	Amounts (g)	Absorbance	Size (nm)
1	Cremophor RH40 Labrasol Capmul MCM	0.50 0.20 0.30	0.016	14.1 (2.5)
2	Tween 20 Lauroglycol Glycofurol	0.67 0.16 0.17	0.039	12.3 (2.1)
3	Cremophor RH40 Arlacel 186 Sodium taurocholate Propylene glycol	0.30 0.20 0.18 0.32	0.004	9.0 (1.6)
4	Cremophor RH40 Span 80 PEG 400	0.54 0.26 0.20	0.167	17.6 (3.8)
5	Cremophor RH40 Arlacel 186 Propylene glycol	0.06 0.62 0.32	2.497	2610 (564)
6	Cremophor RH40 Propylene glycol	0.49 0.51	-0.010	13.8 (2.3)

Note that Sample Nos. 5 and 6 are control samples. Sample No. 5 was observed to form a cloudy emulsion upon mixing with an aqueous diluent, and fails to show a small particle size. Sample No. 6 contains only one surfactant.

## Example 2: Membrane Transport Studies

### Experimental

The membrane transport studies of model hydrophobic therapeutic agents were carried out across the CACO-2 monolayers. The Caco-2 cell line, originating from a human carcinoma, was obtained from the American Type Culture collection and was grown to form confluent monolayers as described elsewhere (I.J. Hidalgo, T.J. Raub, and R.T. Borchardt, *Gastroenterology* 96:736-749 (1989)). All cells used in this study were between 50 and 60 passage number. The cells were measured for confluency by measurement of TEER (trans epithelial electrical resistance) values. Monolayers exhibiting similar TEER values consistent with "non leakiness" were used to study and compare transport characteristics of model actives in plain buffer and in presence of diluted compositions of the present invention.

In duplicate, all transport experiments were performed for 2 hrs at 37°C in pH 7.35 HBSS containing 25 mM glucose and 10 mM Hepes buffer. Prior to the experiments, the culture medium of Transwell grown Caco-2 cell monolayers was replaced with transport medium equilibrated at 37°C, and the cell monolayer was subsequently equilibrated before undertaking transport studies.

Two hydrophilic therapeutic agents, foscarnet and PEG-4000, were tested. Foscarnet sodium is a low molecular weight (192 g/mol) hydrophilic antiviral that inhibits viral DNA polymerase and reverse transcriptase. It is very soluble in water, shows pK<sub>a</sub>s of 0.5, 3.4 and 7.3, and has a log of octanol/water partition coefficient of -2.0 (at pH 7.4). Apical to basal transport of the model hydrophilic actives foscarnet sodium and polyethylene glycol 4000 (PEG-4000) was studied by spiking the transport medium, a plain buffer or a 100X buffer dilution of the composition under investigation, with one micro curie of radio-labeled active on the apical side. Basolateral appearance of the active was monitored by taking appropriate samples and assaying for radioactivity. Permeability coefficients (P) were calculated using the following equation:

$$P = (dQ/dt) / (AC_0)$$

where P is the permeability coefficient, dQ/dt is the flux across the monolayer (DPM/min), A is the surface area of the membrane, and C<sub>0</sub> is the initial concentration of the active.

### Results:

Table 20 shows the apical to basal membrane transport of a conventional hydrophilic active, foscarnet sodium in Sample Nos. 1-3, and a model macromolecular hydrophilic active, PEG-4000, in Sample No. 4, compared to a plain buffer solution

Table 20: Permeability for a Conventional Hydrophilic Active

Sample No.	Active	$(P_{\text{sample}}^a / P_{\text{buffer}}^b) \times 100$
1	foscarnet sodium	1007
2	foscarnet sodium	195
3	foscarnet sodium	160
4	PEG-4000	188

<sup>a</sup> permeability in the presence of 100X diluted composition

<sup>b</sup> permeability in the presence of buffer only

### Example 3: Relative Absorption Study

#### Experimental:

The sample preconcentrate solutions were diluted with standard hypotonic PBS pH 7.4 buffer. Two hydrophilic therapeutic agents were studied: a conventional hydrophilic active, acyclovir, and the model macromolecular active, PEG-4000.

For the acyclovir compositions, the compositions after dilution were spiked with 0.1 mM cold acyclovir, then 0.5 microliter of tritiated acyclovir (specific activity 18.9 Ci/mmol) was added to the diluted composition. The osmotic pressure was adjusted with sodium chloride as needed. The resulting aqueous isotonic dispersions were perfused through rat intestinal segments to assess absorption enhancement in a procedure described below. Appearance of the active was monitored in the mesenteric blood along with disappearance on the luminal side.

Surprisingly, appreciable levels of the conventional hydrophilic active were noted in the blood compared to control perfusion studies conducted with plain buffer and with the control samples 5 (milky emulsion-forming preconcentrate) and 6 (plain one surfactant concentrate), showing that the compositions of the present invention increased absorption characteristics of very hydrophilic actives.

1 For the model macromolecular active, radio labeled PEG-4000 was added to a  
diluted (50X) pre-concentrate, and the resulting clear aqueous isotonic dispersion was  
perfused through a rat intestinal segment to assess absorption enhancement in a procedure  
described below. Appearance of the active was monitored in the mesenteric blood along  
5 with disappearance on the luminal side. Surprisingly, as with the acyclovir, appreciable  
levels of hydrophilic active were noted in the blood compared to control perfusion studies  
conducted with plain buffer, showing the unexpected result that the compositions of the  
present invention increased permeability characteristics of very hydrophilic  
macromolecular actives.

10 Procedure:

Young adult (275-300 g) male Sprague Dawley rats were used. The procedures  
were consistent with those reported by Winne et al., "In vivo studies of mucosal-serosal  
transfer in rat jejunum", *Naunyn-Schmeideberg's Arch. Pharmacol.*, 329, 70 (1985).

15 Jugular vein cannulation: the animal was anesthetized using 2% halothane in 98%  
oxygen via a halothane vaporizer (Vapomatic, A.M. Bickford, Inc., NY). An opening in  
the jugular vein was made with a 21 gauge needle and a jugular cannula consisting of a 4  
cm segment of silastic tubing connected to polyethylene tubing was inserted in the jugular  
vein and secured with cyanoacrylate glue. For the donor rat, approximately 20 mL of  
blood was freshly collected in the presence of heparin (1,000 units) and the collected  
20 blood was infused at a rate of 0.2 mL/min through the jugular vein in the experimental rat  
to replenish blood sampling.

Intestine cannulation: after the animal was anesthetized, its body temperature was  
maintained at 37 °C using a heating pad. A vertical midline incision of approximately 3  
cm was made through the skin to expose the small intestine. Approximately 6-10 cm  
25 segment of ileum was located. Using electro-cautery, a small incision was made at the  
ends of the segment and the luminal contents were flushed with saline maintained at 37  
°C. Two 1.5 cm notched pieces of Teflon tubing were inserted into the intestinal lumen at  
each incision and tightened using 4-0 silk. A warm isotonic buffer was passed through the  
intestine using a 50-mL syringe. These teflon cannula were used to perfuse the drug  
30 solution through the isolated intestinal segment using a syringe pump.

Mesenteric vein cannulation: the mesenteric vein draining blood from the resulting  
isolated mesenteric cascade venule was then cannulated using a 24 gauge IV catheter and



1 secured in place using 4-0 silk sutures. The cannula was then connected to a polyethylene tubing 25 cm long where the blood was collected in a vial kept under the animal level. Blood samples were collected continuously over 60 to 90 min. The infusion of blood via the jugular vein was initiated to replenish blood loss.

5 Results:

I. Conventional Hydrophilic Active (acyclovir)

The experiment was performed twice for each of the test samples and control buffer compositions. For each formulation, the results of the two trials were averaged. The cumulative amount of radioactivity for the duration of the study as a fraction of total radioactivity exposed to the intestinal segment was monitored for each trial to assess absorption. The % relative absorption results for a conventional hydrophilic active (acyclovir) in presence of various diluted example compositions compared to a plain buffer are presented in Table 21. The relative absorption reported in Table 21 is 100 times the ratio of the fraction of the total amount administered in mesenteric blood when perfused with the 25X diluted compositions to the fraction of the total amount administered when perfused with the plain buffer, over the same time period.

Table 21: Relative Absorption of Acyclovir

Sample No.	% Relative Absorption
1	614
2	634
3	704
Control Samples:	
5	171
6	141

Surprisingly, appreciable bioenhancement was observed only for compositions that had at least one hydrophilic surfactant plus a second surfactant, and that formed very small dispersions upon dilution (Sample Nos. 1-3), showing that effective presentation of carrier at the absorption site is very critical. In contrast, compositions that contained the same surfactants but formed larger unstable emulsion upon dilution (Sample No. 5) due to poor choice of concentration, or contained only a single surfactant (Sample No. 6) resulted in only marginal bioenhancement over plain buffer.

## 1 II. Macromolecular Hydrophilic Active

The results for a macromolecular hydrophilic active is presented in Table 22. The experiment was performed twice for each composition. The relative absorption shown in the Table is for a 50X dilution

5 Table 22: Relative Absorption of a Macromolecular Active

Sample No.	% Relative Absorption
3	991

10 In comparison to negligible absorption of PEG 4000 in presence of plain buffer, the absorption of PEG 4000 in the presence of a composition of the present invention gave surprising high absorption. This demonstrates the improved absorption of macromolecules with compositions of the present invention.

Example 4: Absorption Enhancing Carriers

15 Typical surfactant ratios consistent with the invention that can be prepared are listed. Additives can be included as discussed herein, and the concentrations can be varied as desired to render the compositions easy to prepare, stable upon storage, bioacceptable and elegant, provided that the concentrations are such that the carrier forms an aqueous dispersion having a small particle size, upon dilution with an aqueous medium. Adequate enzyme inhibitor, bufferants, other additives and organic solubilizers can be included at pharmaceutically acceptable levels. Hydrophilic therapeutic agents can be added at levels  
20 convenient for therapeutic effect.

A: Compositions Having At least Two Hydrophilic Surfactants

Sodium taurocholate 0.18g  
Cremophor RH 40 0.30g

25 Sodium chenodeoxycholate 0.30g  
Tween 80 0.50g

Sodium Sarcosolate 0.15g  
Crovol M-70 0.60g

30 Sodium lithocholate 0.30g  
Labrasol 0.55g

Sodiun glycocholate 0.10g  
Tween 20 0.50g

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1	Sodium ursodeoxycholate	0.30
	Incrocas-35	0.50
	Chenodeoxycholic acid	0.25g
	Cremophor RH 40	0.50g
5	Cremophor RH 40	0.60g
	Sodium caprate	0.10g
	Cremophor RH 40	0.50g
	Palmitoyl carnitine	0.20g
10	Solulan C-24	0.60g
	Sodium chenodeoxycholate	0.25g
	Taurocholate	0.20g
	Egg or Soy lecithin	0.09g
	Tween 20	0.30g
	Sodium taurocholate	0.20g
15	Tween 20	0.25g
	Egg lecithin	0.15g
	Chenodeoxycholate	0.18g
	C <sub>18</sub> lysolipid	0.10g
20	Chenodeoxycholate	0.20g
	Oleic acid	0.10g
	Labrasol	0.20g
	Brij 35	0.75g

B: Compositions Having One Hydrophilic and One Hydrophobic Surfactant

25	Cremophor EL-P	0.83g
	Peceol	0.17g
	Cremophor EL-P	0.50g
	Propylene glycol monocaprates	0.20g
30	Cremophor EL-P	0.50g
	Imwitor 375	0.20g
	Cremophor EL-P	0.50g
	Nikkol MGM	0.18g
	Cremophor RH 40	0.50g

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1	Arlacel 186	0.10g
	Cremophor RH 40	1.53g
	Arlacel 186	0.38
	HPB cyclodextrin	0.18g
5	Cremophor RH 40	0.55g
	Capmul MCM	0.80g
	Cremophor RH 40	0.50g
	Crodamol (ethyl oleate)	0.28g
10	Cremophor RH 40	0.50g
	Labrafil	0.40g
	Cremophor RH 40	0.22g
	Lauroglycol FCC	0.20g
	Cremophor RH40	0.60g
	Glyceryl monolaurate	0.20g
15	Cremophor RH-40	0.43g
	Myvacet 9-45	0.31g
	Cremophor RH-40	0.30g
	Peceol	0.11g
20	Cremophor RH40	0.50g
	Propyleneglycol monololeate	0.20g
	Cremophor RH40	0.50g
	Softigen 701	0.10g
	Cremophor RH40	0.50g
	Sorbitan monocaprates	0.25g
25	Cremophor RH 60	0.54g
	Span 80	0.26g
	Cremophor RH 40	0.70g
	Volpo 3	0.30g
30	Crodet O40	0.68g
	Plurol Oleique	0.32g
	Crovol M-70	0.61g
	Crovol M-40	0.12g

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1	Crovol M-70	0.38g
	Labrafil	0.60g
	Crovol M-70	0.65g
	Imwitor 988	0.15g
5	Crovol M-70	0.60g
	Linoleic acid	0.20g
	Emalex C-40	0.50g
	Gelucire 33/01	0.15g
10	Glycerol L	0.73g
	Myvacet 9-45	0.27g
	Incrocas 35	0.65g
	Arlacel 186	0.12g
	Incrocas 35	0.25g
	Gelucire 44/14	0.15g
15	Incrocas 35	0.83g
	Imwitor 988	0.20g
	Incrocas 35	0.31g
	Labrafil	0.11g
20	Labrasol	0.83g
	Lauroglycol	0.17g
	Lauroyl carnitine	0.15g
	Imwitor 312	0.15g
	Incrocas 35	0.50g
	Myvacet 9-45	0.38g
25	Incrocas-35	0.50g
	Span-20	0.15g
	Incrocas 35	0.51g
	Imwitor 988	0.22g
30	Kessco PEG 300DL	0.35g
	Gelucire 50/15	0.50g
	Kessco PEG 1540DO	0.65g
	Span 80	0.12

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1	Labrasol	0.45g
	Span-20	0.25g
	Myrj 45	0.50g
	Sorbitan monocaprylate	0.25g
5	Myrj 52	0.50g
	Imwitor 308	0.20g
	Sucrose monolaurate	0.50g
	Capmul MCM	0.20g
10	Nikkol Decaglyn 1-L	0.55g
	Crovol M-40	0.33g
	Nikkol Decaglyn 1-0	0.65g
	Capmul MCM	0.25g
15	Nikkol DHC	0.67g
	Nikkol TMGO-5	0.17g
	Nikkol BPS-30	0.30g
	PEG-6 castor oil	0.15g
20	Tween 20	0.75g
	Drewpol 6-1-0	0.15g
	Tween 20	0.34g
	Lauroglycol FCC	0.11g
25	Tween 20	0.58g
	Plurol Oleique	0.21g
	Tween 80	0.67g
	Lauroglycol	0.17g
30	Tagat O2	0.50g
	PGMG-03	0.05g
	Tagat L2	0.68g
	Brij 30	0.32g
	Poloxamer 188	0.85g
	Labrafil M2125CS	0.15g
	Poloxamer 108	0.85g
	Capmul GMO-K	0.15g



1	Solulan C-24	0.58g
	Lauroglycol FCC	0.21g

C: Two Hydrophilic Surfactants and One Hydrophobic Surfactant

5	Cremophor EL	0.30g
	Labrasol	0.30g
	Capmul MCM	0.40g
	Cremophor RH-40	0.25g
	Labrasol	0.25g
10	Capmul GMO-K	0.11g
	Cremophor RH 40	0.30g
	Tween-20	0.20g
	Nikkol Decaglyn 3-O	0.50g
	Cremophor EL-P	0.45g
15	Corvol M-40	0.25g
	Sodium Docusate	0.15g
	Cremophor RH 40	0.65g
	Arlacel 186	0.15g
	Sodium dodecyl sulfate	0.10g
20	Cremophor RH 40	0.50g
	Peceol	0.20g
	Sodium docusate	0.20g
	Sodium Chenodeoxycholate	0.30g
	Cremophor RH 40	0.40g
	Arlacel 186	0.30g
25	Cremophor RH 40	0.41g
	Sodium taurocholate	0.26g
	Arlacel 186	0.27g
	Cremophor RH 40	0.50g
	Softigen 767	0.22g
	Arlacel 186	0.15 g
30	Cremophor RH 40	0.40g
	Arlacel 186	0.40g
	Tween 20	0.20g

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1	Cremophor RH 40	0.35g
	Capmul MCM	0.30g
	Sodium chenodeoxycholate	0.30g
5	Kessco PEG 1000MO	0.30g
	Labrasol	0.30g
	Span 20	0.40g
	Polaxamer 188	0.65g
	Peceol	0.15g
	Sodium dodecyl sulfate	0.10g
10	Sodium taurocholate	0.17g
	Tween 20	0.66g
	Arlacel 186	0.17g
	Sodium taurocholate	0.17g
	Kessco PEG 1000MO	0.66g
	Plurol Oleique	0.17g
15	Sodium taurocholate	0.15g
	Tween 80	0.18g
	Arlacel 186	0.18g
	Taurochenodeoxycholate	0.15g
	Tween 20	0.40g
	Arlacel 186	0.15g
20	Chenodeoxycholic acid	0.25g
	Incrocas-35	0.30g
	Span 20	0.20g
	Saurcocholate	0.20g
	Cremophor RH 40	0.40g
	Arlacel 186	0.20g
25	Lithocholate	0.25g
	Incrocas-35	0.40g
	Myvacet 9-45	0.30g
	Tagat L2	0.45g
	Crovol A-40	0.25g
	Sodium docusate	0.15g
30	Tween -20	0.30g
	Arlacel 186	0.20g
	Sodium chenodeoxycholate	0.25g

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1	Cremophor RH 40	0.40g
	Tween-20	0.25g
	Sodium caprate	0.25g
5	Cremophor RH40	0.40g
	Lauric acid	0.20g
	Incrocas-35	0.30g

D: One Hydrophilic and Two Hydrophobic Surfactants

10	Cremophor RH 40	0.50g
	Labrafil M2125CS	0.27g
	Crovol M-40	0.28g
15	Cremophor RH 40	1.53g
	Arlacel 186	0.38g
	Peceol	0.38g
	HPB beta cyclodextrin	0.38g
15	Cremophor RH 40	0.55g
	Labrafil M2125 CS	0.34g
	Span 80	0.2g
20	Cremophor RH 40	0.50g
	Labrafil M2125 Cs	0.27g
	Crovol M-40	0.28g

E: Two Hydrophilic and Two Hydrophobic Surfactants

25	Polaxamer 108	0.45g
	Span 20	0.25g
	Sodium docusate	0.15g
	Ethyl oleate	0.15g
25	Softigen 767	0.45g
	Imwitor 742	0.25g
	Sodium docusate	0.15g
	Ethyl oleate	0.15g

Example 5: Compositions with Hydrophilic Therapeutic Agent

30 Typical compositions having a hydrophilic therapeutic agent can have components and concentrations in the following exemplary, but not limiting ranges, in percent by weight unless otherwise indicated:

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1	absorption enhancing composition	10-100%
	enzyme Inhibitor ( <i>e.g.</i> , aprotinin)	0-10%
	solubilizer ( <i>e.g.</i> , propylene glycol)	0-60%
	bufferant	0-50mM
5	hydrophilic polymer ( <i>e.g.</i> , HPMC)	0-20% w/w
	other additives	0-50%

If formulated as an aqueous dosage form, a typical amount of water would be about 250 mL, or any other convenient amount.

Typical hydrophilic therapeutic agents and amounts in mg or IU/mL or G:

10	alendronate Sodium	5-50mg
	etidronate disodium	200-400 mg
	pamidronate disodium	30-90 mg
	aztreonam	20-500 mg
	valacyclovir	250-1000 mg
15	gancyclovir	250-500 mg
	famcyclovir	125-200 mg
	pericyclovir	125-1000 mg
	pyridostigmine	60 mg
	cromalyn sodium	0.1-2mg
20	nedocromil sodium	0.1-2 mg
	metformin hydrochloride	500-850 mg
	acarbose	50-100 mg
	amphotericin B	50-200 mg
	octreotide acetate	0.1 to 1 mg
25	cefoxitin sodium	200-1000 mg
	corticotropin:	25-1000 IU
	sodium heparin	20-5000 IU
	desmopressin acetate (DVAP)	0.1-1mg
	vasopressin	5-100 IU
30	salmon calcitonin	500 IU
	insulin	140 IU
	erythropoietin	14,000 mg

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1           porcine somatotropin           50 mg  
          recombinant growth hormone       30 IU  
          oligonucleotide           1-500 mg

5           Of course, the amounts listed are chosen to be therapeutically effective amounts,  
but the invention is not limited thereby.

          The present invention may be embodied in other specific forms without departing  
from its spirit or essential characteristics. The described embodiments are to be  
considered in all respects only as illustrative and not restrictive. The scope of the  
invention is, therefore, indicated by the appended claims rather than by the foregoing  
10 description. All changes which come within the meaning and range of equivalency of the  
claims are to be embraced within their scope.

          What is claimed is:

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- 1           1.       A pharmaceutical system for enhanced absorption of a hydrophilic  
therapeutic agent, the system comprising:
- (a)     a dosage form of an absorption enhancing composition, the  
composition comprising at least two surfactants, at least one of which is  
5           hydrophilic; and
- (b)     a hydrophilic therapeutic agent,  
the pharmaceutical system being substantially free of triglycerides.
2.     The pharmaceutical system of claim 1, wherein the hydrophilic surfactant  
comprises at least one ionized ionizable surfactant;
- 10           3.     The pharmaceutical system of claim 2, wherein the ionized ionizable  
surfactant is the ionized form of a surfactant selected from the group consisting of bile  
acids and salts, analogues, and derivatives thereof; lecithins, lysolecithin, phospholipids,  
lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of  
alkylsulfates; salts of fatty acids; sodium docusate; acyl lactylates; mono-,diacetylated  
15           tartaric acid esters of mono-,diglycerides; succinylated monoglycerides; citric acid esters  
of mono-,diglycerides; and mixtures thereof.
4.     The pharmaceutical system of claim 2, wherein the ionized ionizable  
surfactant is the ionized form of a surfactant selected from the group consisting of lecithin,  
lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol,  
20           phosphatidic acid, phosphatidylserine, lysophosphatidylcholine,  
lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid,  
lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine,  
lactylic esters of fatty acids, stearyl-2-lactylate, stearyl lactylate, succinylated  
monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid  
25           esters of mono/diglycerides, cholate, taurocholate, glycocholate, deoxycholate,  
taurodeoxycholate, chenodeoxycholate, glycodeoxycholate, glycochenodeoxycholate,  
taurochenodeoxycholate, ursodeoxycholate, lithocholate, tauroursodeoxycholate,  
glycoursodeoxycholate, cholylsarcosine, N-methyl taurocholate, caproate, caprylate,  
30           caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate,  
lauryl sulfate, tetraacetyl sulfate, docusate, lauroyl carnitine, palmitoyl carnitine, myristoyl  
carnitine, and salts and mixtures thereof.



1           5.     The pharmaceutical system of claim 2, wherein the ionized ionizable  
surfactant is the ionized form of a surfactant selected from the group consisting of lecithin,  
lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol,  
lysophosphatidylcholine, PEG-phosphatidylethanolamine, lactic esters of fatty acids,  
5     stearoyl-2-lactylate, stearyl lactylate, succinylated monoglycerides, mono/diacetylated  
tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholate,  
taurocholate, glycocholate, deoxycholate, chenodeoxycholate, lithocholate,  
ursodeoxycholate, taurodeoxycholate, glycodeoxycholate, cholylsarcosine, caproate,  
caprylate, caprate, laurate, oleate, lauryl sulfate, docusate, lauroyl carnitine, palmitoyl  
10    carnitine, myristoyl carnitine, and salts and mixtures thereof.

          6.     The pharmaceutical system of claim 2, wherein the ionized ionizable  
surfactant is the ionized form of a surfactant selected from the group consisting of lecithin,  
lactic esters of fatty acids, stearyl-2-lactylate, stearyl lactylate, succinylated  
monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid  
15    esters of mono/diglycerides, chenodeoxycholate, lithocholate, ursodeoxycholate,  
taurocholate, caprylate, caprate, oleate, lauryl sulfate, docusate, lauroyl carnitine,  
palmitoyl carnitine, myristoyl carnitine, and salts and mixtures thereof.

          7.     The pharmaceutical system of claim 1, wherein the hydrophilic surfactant  
comprises at least one non-ionic hydrophilic surfactant having an HLB value greater than  
20    or equal to about 10.

          8.     The pharmaceutical system of claim 7, wherein the non-ionic surfactant is  
selected from the group consisting of alkylglucosides; alkylmaltosides;  
alkylthioglucosides; lauryl macrogolglycerides; polyoxyethylene alkyl ethers;  
polyoxyethylene alkylphenols; polyethylene glycol fatty acids esters; polyethylene glycol  
25    glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-  
polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene  
glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene  
vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols  
and at least one member of the group consisting of fatty acids, glycerides, vegetable oils,  
30    hydrogenated vegetable oils, and sterols; sugar esters, sugar ethers; sucroglycerides; and  
mixtures thereof.

1           9.     The pharmaceutical system of claim 7, wherein the non-ionic hydrophilic  
surfactant is selected from the group consisting of polyoxyethylene alkylethers;  
polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters;  
polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block  
5 copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene  
vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols  
and at least one member of the group consisting of fatty acids, glycerides, vegetable oils,  
hydrogenated vegetable oils, and sterols; and mixtures thereof.

10           10.    The pharmaceutical system of claim 9, wherein the glyceride is a  
monoglyceride, diglyceride, triglyceride, or a mixture thereof.

11.    The pharmaceutical system of claim 9, wherein the reaction mixture  
comprises the transesterification products of a polyol and at least one member of the group  
consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and  
sterols.

15           12.    The pharmaceutical system of claim 9, wherein the polyol is glycerol,  
ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, a  
saccharide, or a mixture thereof.

13.    The pharmaceutical system of claim 7, wherein the hydrophilic surfactant is  
PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate,  
20 PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200  
oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100  
stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl  
laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-  
30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel  
25 oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor  
oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil,  
PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10  
laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate,  
PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9  
30 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl  
ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10 oleate, Tween  
40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG

1 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, a poloxamer, or a mixture thereof.

14. The pharmaceutical system of claim 7, wherein the hydrophilic surfactant is PEG-20 laurate, PEG-20 oleate, PEG-35 castor oil, PEG-40 palm kernel oil, PEG-40  
5 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, polyglyceryl-10 laurate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, PEG-30 cholesterol, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, PEG-24 cholesterol, sucrose monostearate, sucrose monolaurate, a poloxamer, or a mixture thereof.

10 15. The pharmaceutical system of claim 7, wherein the hydrophilic surfactant is PEG-35 castor oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polysorbate 20, polysorbate 80, tocopheryl PEG-1000 succinate, PEG-24 cholesterol, a poloxamer, or a mixture thereof.

15 16. The pharmaceutical system of claim 1, wherein the composition comprises at least two hydrophilic surfactants.

17. The pharmaceutical system of claim 1, wherein the composition comprises at least one hydrophilic surfactant and at least one hydrophobic surfactant.

18. The pharmaceutical system of claim 17, wherein the hydrophobic  
20 surfactant comprises an un-ionized ionizable surfactant.

19. The pharmaceutical system of claim 18, wherein the un-ionized ionizable surfactant is the un-ionized form of a surfactant selected from the group consisting of bile acids and analogues and derivatives thereof; lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid esters; alkylsulfates; fatty  
25 acids; acyl lactylates; mono-,diacetylated tartaric acid esters of mono-,diglycerides; succinylated monoglycerides; citric acid esters of mono-,diglycerides; and mixtures thereof.

20. The pharmaceutical system of claim 18, wherein the un-ionized ionizable surfactant is the un-ionized form of a surfactant selected from the group consisting of  
30 lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid,

1 lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine,  
lactylic esters of fatty acids, stearyl-2-lactylate, stearyl lactylate, succinylated  
monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid  
esters of mono/diglycerides, cholic acid, taurocholic acid, glycocholic acid, deoxycholic  
5 acid, taurodeoxycholic acid, chenodeoxycholic acid, glycodeoxycholic acid,  
glycochenodeoxycholic acid, taurochenodeoxycholic acid, ursodeoxycholic acid,  
lithocholic acid, tauroursodeoxycholic acid, glyoursodeoxycholic acid, cholylsarcosine,  
N-methyl taurocholic acid, caproic acid, caprylic acid, capric acid, lauric acid, myristic  
acid, palmitic acid, oleic acid, ricinoleic acid, linoleic acid, linolenic acid, stearic acid,  
10 lauryl sulfate, tetraacetyl sulfate, lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine,  
and mixtures thereof.

21. The pharmaceutical system of claim 18, wherein the un-ionized ionizable  
surfactant is the un-ionized form of a surfactant selected from the group consisting of  
lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine,  
15 phosphatidylglycerol, lysophosphatidylcholine, PEG-phosphatidylethanolamine, lactylic  
esters of fatty acids, stearyl-2-lactylate, stearyl lactylate, succinylated monoglycerides,  
mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of  
mono/diglycerides, cholic acid, taurocholic acid, glycocholic acid, deoxycholic acid,  
chenodeoxycholic acid, lithocholic acid, ursodeoxycholic acid, taurodeoxycholic acid,  
20 glycodeoxycholic acid, cholylsarcosine, caproic acid, caprylic acid, capric acid, lauric  
acid, oleic acid, lauryl sulfate, lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine,  
and mixtures thereof.

22. The pharmaceutical system of claim 18, wherein the un-ionized ionizable  
surfactant is the un-ionized form of a surfactant selected from the group consisting of  
25 lecithin, lactylic esters of fatty acids, stearyl-2-lactylate, stearyl lactylate, succinylated  
monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid  
esters of mono/diglycerides, chenodeoxycholic acid, lithocholic acid, ursodeoxycholic  
acid, taurocholic acid, caprylic acid, capric acid, oleic acid, lauryl sulfate, docusate,  
lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine, and mixtures thereof.

23. The pharmaceutical system of claim 17 wherein the hydrophobic surfactant  
30 comprises at least one compound having an HLB value less than about 10.

1           24. The pharmaceutical system of claim 23, wherein the hydrophobic  
surfactant is selected from the group consisting of alcohols; polyoxyethylene alkylethers;  
fatty acids; bile acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower  
alcohol fatty acids esters; polyethylene glycol fatty acids esters; polyethylene glycol  
5 glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene  
glycerides; lactic acid derivatives of mono/diglycerides; propylene glycol diglycerides;  
sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-  
polyoxypropylene block copolymers; transesterified vegetable oils; sterols; sterol  
derivatives; sugar esters; sugar ethers; sucroglycerides; polyoxyethylene vegetable oils;  
10 polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one  
member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated  
vegetable oils, and sterols; and mixtures thereof.

          25. The pharmaceutical system of claim 23, wherein the hydrophobic  
surfactant is selected from the group consisting of fatty acids; bile acids; lower alcohol  
15 fatty acid esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty  
acid esters; polyoxyethylene glycerides; glycerol fatty acid esters; acetylated glycerol fatty  
acid esters; lactic acid derivatives of mono/diglycerides; sorbitan fatty acid esters;  
polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block  
copolymers; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable  
20 oils; reaction mixtures of polyols and at least one member of the group consisting of fatty  
acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures  
thereof.

          26. The pharmaceutical system of claim 23, wherein the hydrophobic  
surfactant is selected from the group consisting of bile acids; lower alcohol fatty acids  
25 esters; polypropylene glycol fatty acid esters; propylene glycol fatty acid esters; glycerol  
fatty acid esters; acetylated glycerol fatty acid esters; lactic acid derivatives of  
mono/diglycerides; sorbitan fatty acid esters; polyoxyethylene vegetable oils; and mixtures  
thereof.

          27. The pharmaceutical system of claim 23, wherein the hydrophobic  
30 surfactant is a glycerol fatty acid ester, an acetylated glycerol fatty acid ester, or a mixture  
thereof.



1           28.    The pharmaceutical system of claim 27, wherein the glycerol fatty acid ester is a monoglyceride, diglyceride, or a mixture thereof.

          29.    The pharmaceutical system of claim 28, wherein the fatty acid of the glycerol fatty acid ester is a C<sub>6</sub> to C<sub>22</sub> fatty acid or a mixture thereof.

5           30.    The pharmaceutical system of claim 23, wherein the hydrophobic surfactant is a reaction mixture of a polyol and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

          31.    The pharmaceutical system of claim 30, wherein the reaction mixture is a transesterification product of a polyol and at least one member of the group consisting of  
10 fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

          32.    The pharmaceutical system of claim 30, wherein the polyol is polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, a saccharide, or a mixture thereof.

          33.    The pharmaceutical system of claim 23, wherein the hydrophobic surfactant is selected from the group consisting of myristic acid; oleic acid; lauric acid;  
15 stearic acid; palmitic acid; PEG 1-4 stearate; PEG 2-4 oleate; PEG-4 dilaurate; PEG-4 dioleate; PEG-4 distearate; PEG-6 dioleate; PEG-6 distearate; PEG-8 dioleate; PEG 3-16 castor oil; PEG 5-10 hydrogenated castor oil; PEG 6-20 corn oil; PEG 6-20 almond oil; PEG-6 olive oil; PEG-6 peanut oil; PEG-6 palm kernel oil; PEG-6 hydrogenated palm kernel oil; PEG-4 capric/caprylic triglyceride, mono, di, tri, tetra esters of vegetable oil  
20 and sorbitol; pentaerythrityl di, tetra stearate, isostearate, oleate, caprylate, or caprate; polyglyceryl 2-4 oleate, stearate, or isostearate; polyglyceryl 4-10 pentaoleate; polyglyceryl-3 dioleate; polyglyceryl-6 dioleate; polyglyceryl-10 trioleate; polyglyceryl-3 distearate; propylene glycol mono- or diesters of a C<sub>6</sub> to C<sub>22</sub> fatty acid; monoglycerides of a C<sub>6</sub> to C<sub>22</sub> fatty acid; acetylated monoglycerides of C<sub>6</sub> to C<sub>22</sub> fatty acid; diglycerides of C<sub>6</sub>  
25 to C<sub>22</sub> fatty acids; lactic acid derivatives of monoglycerides; lactic acid derivatives of diglycerides; cholesterol; phytosterol; PEG 5-20 soya sterol; PEG-6 sorbitan tetra, hexastearate; PEG-6 sorbitan tetraoleate; sorbitan monolaurate; sorbitan monopalmitate; sorbitan mono, trioleate; sorbitan mono, tristearate; sorbitan monoisostearate; sorbitan sesquioleate; sorbitan sesquistearate; PEG 2-5 oleyl ether; POE 2-4 lauryl ether; PEG-2  
30 cetyl ether; PEG-2 stearyl ether; sucrose distearate; sucrose dipalmitate; ethyl oleate; isopropyl myristate; isopropyl palmitate; ethyl linoleate; isopropyl linoleate; poloxamers;



1 cholic acid; ursodeoxycholic acid; glycocholic acid; taurocholic acid; lithocholic acid;  
deoxycholic acid; chenodeoxycholic acid; and mixtures thereof.

34. The pharmaceutical system of claim 23, wherein the hydrophobic  
surfactant is selected from the group consisting of oleic acid; lauric acid; glyceryl  
5 monocaprates; glyceryl monocaprylates; glyceryl monolaurates; glyceryl monooleates;  
glyceryl dicaprates; glyceryl dicaprylates; glyceryl dilaurates; glyceryl dioleates; acetylated  
monoglycerides; propylene glycol oleate; propylene glycol laurate; polyglyceryl-3 oleate;  
polyglyceryl-6 dioleate; PEG-6 corn oil; PEG-20 corn oil; PEG-20 almond oil; sorbitan  
monooleate; sorbitan monolaurate; POE-4 lauryl ether; POE-3 oleyl ether; ethyl oleate;  
10 poloxamers; cholic acid; ursodeoxycholic acid; glycocholic acid; taurocholic acid;  
lithocholic acid; deoxycholic acid; chenodeoxycholic acid; and mixtures thereof.

35. The pharmaceutical system of claim 1, wherein each of the at least two  
surfactants is selected from the group consisting of sodium lauryl sulfate, oleic acid,  
linoleic acid, monoolein, lecithin, lysolecithin, deoxycholate, taurodeoxycholate,  
15 glycochenodeoxycholate, polyoxyethylene X-lauryl ether, where X is from 9 to 20,  
sodium tauro-24,25-dihydrofusidate, polyoxyethylene ether, polyoxyethylene sorbitan  
esters, p-t-octylphenoxypolyoxyethylene, N-lauryl- $\beta$ -D-maltopyranoside, 1-  
dodecylazacycloheptane-2-azone, and phospholipids, and is present in an amount of  
greater than 10% by weight, based on the total weight of the pharmaceutical system.

20 36. The pharmaceutical system of claim 1, wherein the hydrophilic therapeutic  
agent is a drug, a vitamin, a nutritional supplement, a cosmeceutical, a diagnostic agent, or  
a mixture thereof.

37. The pharmaceutical system of claim 1, wherein the hydrophilic therapeutic  
agent has an apparent water solubility of at least about 1 mg/mL.

25 38. The pharmaceutical system of claim 1, wherein the hydrophilic therapeutic  
agent is a hydrophilic drug, a cytokine, a peptidomimetic, a peptide, a protein, a toxoid, a  
serum, an antibody, a vaccine, a nucleoside, a nucleotide, a portion of genetic material, a  
nucleic acid, or a mixture thereof.

30 39. The pharmaceutical system of claim 1, wherein the hydrophilic therapeutic  
agent is selected from the hydrophilic members of the group consisting of analgesics, anti-  
inflammatory agents, anthelmintics, anti-arrhythmic agents, anti-asthma agents, anti-  
bacterial agents, anti-viral agents, anti-coagulants, anti-depressants, anti-diabetics, anti-

1 epileptics, anti-fungal agents, anti-gout agents, anti-hypertensive agents, anti-malarials,  
anti-migraine agents, anti-muscarinic agents, anti-neoplastic agents, immunosuppressants,  
anti-protozoal agents, anti-thyroid agents, anti-tussives, anxiolytic, sedatives, hypnotics,  
neuroleptics,  $\beta$ -Blockers, cardiac inotropic agents, corticosteroids, diuretics, anti-  
5 parkinsonian agents, gastro-intestinal agents, histamine H<sub>2</sub>-receptor antagonists,  
keratolytics, lipid regulating agents, muscle relaxants, anti-anginal agents, nutritional  
agents, analgesics, sex hormones, stimulants, cytokines, peptidomimetics, peptides,  
proteins, toxoids, sera, antibodies, vaccines, nucleosides, nucleotides, genetic material,  
nucleic acids, and mixtures thereof.

10 40. The pharmaceutical system of claim 1, wherein the hydrophilic therapeutic  
agent is selected from the group consisting of acarbose; acyclovir; acetyl cysteine;  
acetylcholine chloride; alatrofloxacin; alendronate; alglucerase; amantadine  
hydrochloride; ambenomium; amifostine; amiloride hydrochloride; aminocaproic acid;  
amphotericin B; antihemophilic factor (human); antihemophilic factor (porcine);  
15 antihemophilic factor (recombinant); aprotinin; asparaginase; atenolol; atracurium  
besylate; atropine; azithromycin; aztreonam; BCG vaccine; bacitracin; becalermine;  
belladonna; bepridil hydrochloride; bleomycin sulfate; calcitonin human; calcitonin salmon;  
carboplatin; capecitabine; capreomycin sulfate; cefamandole nafate; cefazolin sodium;  
cefepime hydrochloride; cefixime; cefonicid sodium; cefoperazone; cefotetan disodium;  
20 cefotaxime; cefoxitin sodium; ceftizoxime; ceftriaxone; cefuroxime axetil; cephalixin;  
cephapirin sodium; cholera vaccine; chorionic gonadotropin; cidofovir; cisplatin;  
cladribine; clidinium bromide; clindamycin and clindamycin derivatives; ciprofloxacin;  
clondronate; colistimethate sodium; colistin sulfate; corticotropin; cosyntropin; cromalyn  
sodium; cytarabine; daltaperin sodium; danaproid; deforoxamine; denileukin diftitox;  
25 desmopressin; diatrizoate meglumine and diatrizoate sodium; dicyclomine; didanosine;  
dirithromycin; dopamine hydrochloride; dornase alpha; doxacurium chloride; doxorubicin;  
editronate disodium; elanaprilat; enkephalin; enoxacin; enoxaprin sodium; ephedrine;  
epinephrine; epoetin alpha; erythromycin; esmol hydrochloride; factor IX; famciclovir;  
fludarabine; fluoxetine; foscarnet sodium; ganciclovir; granulocyte colony stimulating  
30 factor; granulocyte-macrophage stimulating factor; growth hormones- recombinant  
human; growth hormone- bovine; gentamycin; glucagon; glycopyrolate; gonadotropin  
releasing hormone and synthetic analogs thereof; GnRH; gonadorelin; grepafloxacin;

1 hemophilus B conjugate vaccine; Hepatitis A virus vaccine inactivated; Hepatitis B virus  
 vaccine inactivated; heparin sodium; indinavir sulfate; influenza virus vaccine;  
 interleukin-2; interleukin-3; insulin-human; insulin lispro; insulin procine; insulin NPH;  
 insulin aspart; insulin glargine; insulin detemir; interferon alpha; interferon beta;  
 5 ipratropium bromide; isofosfamide; japanese encephalitis virus vaccine; lamivudine;  
 leucovorin calcium; leuprolide acetate; levofloxacin; lincomycin and lincomycin  
 derivatives; lobucavir; lomefloxacin; loracarbef; mannitol; measles virus vaccine;  
 meningococcal vaccine; menotropins; mephenzolate bromide; mesalmine; methanamine;  
 methotrexate; methscopolamine; metformin hydrochloride; metoprolol; mezocillin  
 10 sodium; mivacurium chloride; mumps viral vaccine; nedocromil sodium; neostigmine  
 bromide; neostigmine methyl sulfate; neutontin; norfloxacin; octreotide acetate; ofloxacin;  
 olpadronate; oxytocin; pamidronate disodium; pancuronium bromide; paroxetine;  
 pefloxacin; pentamidine isethionate; pentostatin; pentoxifylline; periciclovir;  
 pentagastrin; phentolamine mesylate; phenylalanine; physostigmine salicylate; plague  
 15 vaccine; piperacillin sodium; platelet derived growth factor-human; pneumococcal vaccine  
 polyvalent; poliovirus vaccine inactivated; poliovirus vaccine live (OPV); polymixin B  
 sulfate; pralidoxine chloride; pramlintide; pregabalin; propofenone; propenthaline  
 bromide; pyridostigmine bromide; rabies vaccine; residronate; ribavarin; rimantadine  
 hydrochloride; rotavirus vaccine; salmetrol xinafoate; sincalide; small pox vaccine;  
 20 solatol; somatostatin; sparfloxacin; spectinomycin; stavudine; streptokinase; streptozocin;  
 suxamethonium chloride; tacrine hydrochloride; terbutaline sulfate; thiopeta; ticarcillin;  
 tiludronate; timolol; tissue type plasminogen activator; TNFR:Fc; TNK-tPA; trandolapril;  
 trimetrexate gluconate; trospectinomycin; trovafloxacin; tubocurarine chloride; tumor  
 necrosis factor; typhoid vaccine live; urea; urokinase; vancomycin; valaciclovir; valsartan;  
 25 varicella virus vaccine live; vasopressin and vasopressin derivatives; vecoronium bromide;  
 vinblastin; vincristine; vinorelbine; vitamin B12 ; warfarin sodium; yellow fever vaccine;  
 zalcitabine; zanamavir; zoladronate; and zidovudine.

41. The pharmaceutical system of claim 1, wherein the hydrophilic therapeutic  
 agent is selected from the group consisting of acarbose; acyclovir; atracurium besylate;  
 30 alendronate; alglucerase; amantadine hydrochloride; amphotericin B; antihemophilic  
 factor (human); antihemophilic factor (porcine); antihemophilic factor (recombinant;  
 azithromycin; calcitonin human; calcitonin salmon; capecitabine; cefazolin sodium;

1 cefonicid sodium; cefoperazone; cefoxitin sodium; ceftizoxime; ceftriaxone; cefuroxime  
axetil; cephalixin; chrionic gonadotropin; cidofovir; cladribine ; clindamycin and  
clindamycin derivatives; cortocotropin; cosyntropin; cromalyn sodium; cytarabine;  
5 daltaperin sodium; danaproid; desmopressin; didanosine; dirithromycin; editronate  
disodium; enoxaprin sodium; epoetin alpha; factor IX; famciclovir; fludarabine; foscarnet  
sodium; ganciclovir; granulocyte colony stimulating factor; granulocyte-macrophage  
stimulating factor; growth hormones- recombinant human; growth hormone- Bovine;  
gentamycin; glucagon; gonadotropin releasing hormone and synthetic analogs thereof;  
GnRH; gonadorelin; hemophilus B conjugate vaccine; Hepatitis A virus vaccine  
10 inactivated; Hepatitis B virus vaccine inactivated; heparin sodium; indinavir sulfate;  
influenza virus vaccine; interleukin-2; interleukin-3; insulin-human; insulin lispro; insulin  
procine; insulin NPH; insulin aspart; insulin glargine; insulin detemir; interferon alpha;  
interferon beta; ipratropium bromide; isofosfamide; lamivudine; leucovorin calcium;  
leuprolide acetate; lincomycin and lincomycin derivatives; metformin hydrochloride;  
15 nedocromil sodium; neostigmine bromide; neostigmine methyl sulfate; neutontin;  
octreotide acetate; olpadronate; pamidronate disodium; pancuronium bromide;  
pentamindine isethionate; pentagastrin; physostigmine salicylate; poliovirus vaccine live  
(OPV); pyridostigmine bromide; residronate; ribavarin; rimantadine hydrochloride;  
rotavirus vaccine; salmetrol xinafoate; somatostatin; spectinomycin; stavudine;  
20 streptokinase; ticarcillin; tiludronate; tissue type plasminogen activator; TNFR:Fc; TNK-  
tPA; trimetrexate gluconate; trospectinomycin; tumor necrosis factor; typhoid vaccine  
live; urokinase; vancomycin; valaciclovir; vasopressin and vasopressin derivatives;  
vinblastin; vincristine; vinorelbine; warfarin sodium; zalcitabine; zanamavir; and  
zidovudine.

25 42. The pharmaceutical system of claim 1, wherein the hydrophilic therapeutic  
agent is selected from the group consisting of acarbose; alendronate; amantadine  
hydrochloride; azithromycin; calcitonin human; calcitonin salmon; ceftriaxone;  
cefuroxime axetil; chrionic gonadotropin; cromalyn sodium; daltaperin sodium;  
danaproid; desmopressin; didanosine; editronate disodium; enoxaprin sodium; epoetin  
30 alpha; factor IX; famciclovir; foscarnet sodium; ganciclovir; granulocyte colony  
stimulating factor; granulocyte-macrophage stimulating factor; growth hormones-  
recombinant human; growth hormone- Bovine; glucagon; gonadotropin releasing hormone

1 and synthetic analogs thereof; GnRH; gonadorelin; heparin sodium; indinavir sulfate;  
influenza virus vaccine; interleukin-2; interleukin-3; insulin-human; insulin lispro; insulin  
procine interferon alpha; interferon beta; leuprolide acetate; metformin hydrochloride;  
nedocromil sodium; neostigmine bromide; neostigmine methyl sulfate; neutontin;  
5 octreotide acetate; olpadronate; pamidronate disodium; residronate; rimantadine  
hydrochloride; salmetrol xinafoate; somatostatin; stavudine; ticarcillin; tiludronate; tissue  
type plasminogen activator; TNFR:Fc; TNK-tPA; tumor necrosis factor; typhoid vaccine  
live; vancomycin; valaciclovir; vasopressin and vasopressin derivatives; zalcitabine;  
zanamavir and zidovudine.

10 43. The pharmaceutical system of claim 1, wherein the composition further  
comprises a solubilizer.

44. The pharmaceutical system of claim 43, wherein the solubilizer is selected  
from the group consisting of alcohols, polyols, amides, esters, propylene glycol ethers and  
mixtures thereof.

15 45. The pharmaceutical system of claim 1, wherein the composition further  
comprises an antioxidant, a bufferant, an antifoaming agent, a detackifier, a preservative, a  
chelating agent, a viscomodulator, a tonicifier, a flavorant, a colorant, an odorant, an  
opacifier, a suspending agent, a binder, a filler, a plasticizer, a lubricant, or a mixture  
thereof.

20 46. The pharmaceutical system of claim 1, wherein the composition further  
comprises an amount of an enzyme inhibiting agent sufficient to at least partially inhibit  
enzymatic degradation of the hydrophilic therapeutic agent.

25 47. The pharmaceutical system of claim 46, wherein the enzyme inhibiting  
agent is P-aminobenzamidine, FK-448, camostat mesylate, sodium glycocholate, an amino  
acid, a modified amino acid, a peptide, a modified peptide, a polypeptide protease  
inhibitor, a complexing agent, a mucoadhesive polymer, a polymer-inhibitor conjugate, or  
a mixture thereof.

30 48. The pharmaceutical system of claim 46, wherein the enzyme inhibiting  
agent is selected from the group consisting of P-aminobenzamidine, FK-448, camostat  
mesylate, sodium glycocholate, aminoboronic acid derivatives, n-acetylcysteine,  
bacitracin, phosphinic acid dipeptide derivatives, pepstatin, antipain, leupeptin,  
chymostatin, elastatin, bestatin, hosphoramindon, puromycin, cytochalasin potatocarboxy



1 peptidase inhibitor, amastatin, protinin, Bowman-Birk inhibitor, soybean trypsin inhibitor,  
chicken egg white trypsin inhibitor, chicken ovomucoid inhibitor, human pancreatic trypsin  
inhibitor, EDTA, EGTA, 1,10-phenanthroline, hydroxyquinoline, polyacrylate derivatives,  
chitosan, cellulose, chitosan-EDTA, chitosan-EDTA-antipain, polyacrylic acid-  
5 bacitracin, carboxymethyl cellulose-pepstatin, polyacrylic acid-Bowman-Birk inhibitor,  
and mixtures thereof.

49. The pharmaceutical system of claim 1, wherein the composition further  
comprises an aqueous medium comprising water, an aqueous palatable diluent or an  
aqueous beverage.

10 50. The pharmaceutical system of claim 49, wherein the therapeutic agent is  
provided to the system in the aqueous medium.

51. The pharmaceutical system of claim 49, wherein the aqueous medium  
further comprises an amount of an enzyme inhibiting agent sufficient to at least partially  
inhibit enzymatic degradation of the hydrophilic therapeutic agent, the enzyme inhibiting  
15 agent being solubilized, suspended, or partially solubilized and partially suspended, in the  
aqueous medium.

52. The pharmaceutical system of claim 1, wherein the composition further  
comprises a pharmaceutically acceptable acid.

53. The pharmaceutical system of claim 52, wherein the acid is selected from  
20 the group consisting of hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid,  
carbonic acid, nitric acid, boric acid, phosphoric acid, acetic acid, acrylic acid, adipic acid,  
alginate acid, alkanesulfonic acid, an amino acid, ascorbic acid, benzoic acid, boric acid,  
butyric acid, carbonic acid, citric acid, a fatty acid, formic acid, fumaric acid, gluconic  
acid, hydroquinonesulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic  
25 acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid,  
salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid,  
toluenesulfonic acid, uric acid, and mixtures thereof.

54. The pharmaceutical system of claim 1, wherein the composition further  
comprises a pharmaceutically acceptable base.

30 55. The pharmaceutical system of claim 54, wherein the base is an amino acid,  
an amino acid ester, ammonium hydroxide, potassium hydroxide, sodium hydroxide,  
sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium



1 hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic  
hydrotalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine,  
ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, or a salt of a  
pharmaceutically acceptable cation and acetic acid, acrylic acid, adipic acid, alginic acid,  
5 alkanesulfonic acid, an amino acid, ascorbic acid, benzoic acid, boric acid, butyric acid,  
carbonic acid, citric acid, a fatty acid, formic acid, fumaric acid, gluconic acid,  
hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid,  
oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid,  
salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid,  
10 toluenesulfonic acid, and uric acid, or a mixture thereof.

56. The pharmaceutical system of claim 1, wherein the at least two surfactants  
are present in amounts such that the composition forms an aqueous dispersion having an  
average particle size of less than about 200 nm upon mixing with an aqueous diluent.

57. The pharmaceutical system of claim 56, wherein the average particle size is  
15 less than about 100 nm.

58. The pharmaceutical system of claim 56, wherein the average particle size is  
less than about 50 nm.

59. The pharmaceutical system of claim 1, wherein the at least two surfactants  
are present in amounts such that the composition forms a substantially optically clear  
20 aqueous dispersion upon mixing with an aqueous diluent.

60. The pharmaceutical system of claim 1, wherein the system is substantially  
free of polyethylene glycol diesters.

61. The pharmaceutical system of claim 1, wherein the system is substantially  
free of cholesterol.

25 62. The pharmaceutical system of claim 1, wherein the dosage form is  
substantially free of water.

63. The pharmaceutical system of claim 1 in the form of a preconcentrate in a  
liquid, semi-solid, or solid form, or as an aqueous or organic diluted preconcentrate.

30 64. The pharmaceutical system of claim 1, wherein the dosage form of the  
composition is processed by balling, lyophilization, encapsulation, extruding,  
compression, melting, molding, spraying, spray congealing, coating, comminution,

1 mixing, cryopelletization, spheronization, homogenization, sonication, granulation, or a combination thereof.

65. The pharmaceutical system of claim 1, wherein the dosage form of the composition of is as a pill, capsule, caplet, tablet, granule, pellet, bead or powder.

5 66. The pharmaceutical system of claim 1, wherein the dosage form of the composition is a starch capsule, a cellulosic capsule, a hard gelatin capsule or a soft gelatin capsule.

67. The pharmaceutical system of claim 1, wherein the dosage form is formulated for immediate release, controlled release, extended release, delayed release, 10 targeted release, or targeted delayed release.

68. The pharmaceutical system of claim 65, which further comprises at least one enteric coating, seal coating, extended release coating, or targeted delayed release coating.

69. The pharmaceutical system of claim 68, wherein the coating is formed of a 15 material selected from the group consisting of shellac, acrylic polymers, cellulosic derivatives, polyvinyl acetate phthalate, and mixtures thereof.

70. The pharmaceutical system of claim 68, wherein the coating is formed of a material selected from the group consisting of Eudragit E, Eudragit L, Eudragit S, Eudragit RL, Eudragit RS, Eudragit NE, Eudragit L.RTM, Eudragit L300.RTM, Eudragit 20 S.RTM, Eudragit L100-55RTM, cellulose acetate phthalate, Aquateric, cellulose acetate trimellitate, ethyl cellulose, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose succinate, polyvinylacetate phthalate, Cotteric, and mixtures thereof.

71. The pharmaceutical system of claim 68, wherein the coating is formed of a material selected from the group consisting of Eudragit L.RTM, Eudragit L300.RTM, 25 Eudragit S.RTM, Eudragit L100-55RTM, cellulose acetate phthalate, Aquateric, ethyl cellulose, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose succinate, polyvinylacetate phthalate, Cotteric, and mixtures thereof.

72. The pharmaceutical system of claim 1, wherein the dosage form of the composition is a solution, suspension, emulsion, cream, ointment, lotion, suppository, 30 spray, aerosol, paste, gel, drops, douche, ovule, wafer, troche, cachet, syrup or elixir.

73. The pharmaceutical system of claim 1, wherein the dosage form is a multiparticulate carrier coated onto a substrate with the composition.

1           74.    The pharmaceutical system of claim 73, wherein the substrate is a particle,  
a granule, a pellet or a bead, and is formed of the therapeutic agent, a pharmaceutically  
acceptable material, or a mixture thereof.

5           75.    The pharmaceutical system of claim 73, wherein the multiparticulate carrier  
is coated with at least one enteric coating, seal coating, extended release coating, or  
targeted delayed release coating.

          76.    The pharmaceutical system of claim 73, wherein the dosage form is further  
processed by encapsulation, compression, extrusion, molding, spheronization or  
cryopelletization.

10          77.    The pharmaceutical system of claim 73, wherein the dosage form is further  
processed to form a starch capsule, a cellulosic capsule, a hard gelatin capsule, or a soft  
gelatin capsule.

          78.    The pharmaceutical system of claim 77, wherein the capsule is coated with  
at least one enteric coating, seal coating, extended release coating, or targeted delayed  
15 release coating.

          79.    The pharmaceutical system of claim 1, wherein the hydrophilic therapeutic  
agent is present in the dosage form of the composition.

          80.    The pharmaceutical system of claim 79, wherein the hydrophilic  
therapeutic agent is solubilized in the composition, suspended in the composition, or  
20 partially solubilized and partially suspended in the composition.

          81.    The pharmaceutical system of claim 1, wherein the hydrophilic therapeutic  
agent is present in a dosage form separate from the dosage form of the composition.

          82.    The pharmaceutical system of claim 1, wherein the dosage form of the  
composition is formulated for oral, mucosal, nasal, pulmonary, vaginal, transmembrane,  
25 buccal or rectal administration.

          83.    The pharmaceutical system of claim 81, wherein the dosage form of the  
hydrophilic therapeutic agent is formulated for oral, mucosal, nasal, pulmonary, vaginal,  
transmembrane, buccal or rectal administration.

          84.    A pharmaceutical system for enhanced absorption of a hydrophilic  
30 therapeutic agent, the system comprising:

1 (a) a dosage form of an absorption enhancing composition, the composition comprising at least one hydrophilic surfactant and at least one hydrophobic surfactant; and

(b) a hydrophilic therapeutic agent,  
5 the pharmaceutical system being substantially free of triglycerides.

85. The pharmaceutical system of claim 84, wherein the hydrophilic surfactant comprises at least one ionized ionizable surfactant;

86. The pharmaceutical system of claim 85, wherein the ionized ionizable surfactant is the ionized form of a surfactant selected from the group consisting of bile  
10 acids and salts, analogues, and derivatives thereof; lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; salts of fatty acids; sodium docusate; acyl lactylates; mono-,diacetylated tartaric acid esters of mono-,diglycerides; succinylated monoglycerides; citric acid esters of mono-,diglycerides; and mixtures thereof.

15 87. The pharmaceutical system of claim 85, wherein the ionized ionizable surfactant is the ionized form of a surfactant selected from the group consisting of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid,  
20 lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactic esters of fatty acids, stearyl-2-lactylate, stearyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholate, taurocholate, glycocholate, deoxycholate, taurodeoxycholate, chenodeoxycholate, glycodeoxycholate, glycochenodeoxycholate,  
25 taurochenodeoxycholate, ursodeoxycholate, lithocholate, tauroursodeoxycholate, glyoursodeoxycholate, cholylsarcosine, N-methyl taurocholate, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, tetraacetyl sulfate, docusate, lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine, and salts and mixtures thereof.

30 88. The pharmaceutical system of claim 85, wherein the ionized ionizable surfactant is the ionized form of a surfactant selected from the group consisting of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol,

1 lysophosphatidylcholine, PEG-phosphatidylethanolamine, lactic esters of fatty acids,  
stearoyl-2-lactylate, stearyl lactylate, succinylated monoglycerides, mono/diacetylated  
tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholate,  
taurocholate, glycocholate, deoxycholate, chenodeoxycholate, lithocholate,  
5 ursodeoxycholate, taurodeoxycholate, glycodeoxycholate, cholylsarcosine, caproate,  
caprylate, caprate, laurate, oleate, lauryl sulfate, docusate, lauroyl carnitine, palmitoyl  
carnitine, myristoyl carnitine, and salts and mixtures thereof.

89. The pharmaceutical system of claim 85, wherein the ionized ionizable  
surfactant is the ionized form of a surfactant selected from the group consisting of lecithin,  
10 lactic esters of fatty acids, stearyl-2-lactylate, stearyl lactylate, succinylated  
monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid  
esters of mono/diglycerides, chenodeoxycholate, lithocholate, ursodeoxycholate,  
taurocholate, caprylate, caprate, oleate, lauryl sulfate, docusate, lauroyl carnitine,  
palmitoyl carnitine, myristoyl carnitine, and salts and mixtures thereof.

15 90. The pharmaceutical system of claim 84, wherein the hydrophilic surfactant  
comprises at least one non-ionic hydrophilic surfactant having an HLB value greater than  
or equal to about 10.

91. The pharmaceutical system of claim 90, wherein the non-ionic surfactant is  
selected from the group consisting of alkylglucosides; alkylmaltosides;  
20 alkylthioglucosides; lauryl macrogolglycerides; polyoxyethylene alkyl ethers;  
polyoxyethylene alkylphenols; polyethylene glycol fatty acids esters; polyethylene glycol  
glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-  
polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene  
glycerides; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylene  
25 vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols  
and at least one member of the group consisting of fatty acids, glycerides, vegetable oils,  
hydrogenated vegetable oils, and sterols; sugar esters, sugar ethers; sucroglycerides; and  
mixtures thereof.

92. The pharmaceutical system of claim 90, wherein the non-ionic hydrophilic  
30 surfactant is selected from the group consisting of polyoxyethylene alkylethers;  
polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters;  
polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block



1 copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

5 93. The pharmaceutical system of claim 92, wherein the glyceride is a monoglyceride, diglyceride, triglyceride, or a mixture thereof.

94. The pharmaceutical system of claim 92, wherein the reaction mixture comprises the transesterification products of a polyol and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

95. The pharmaceutical system of claim 92, wherein the polyol is glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, a saccharide, or a mixture thereof.

96. The pharmaceutical system of claim 90, wherein the hydrophilic surfactant is PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10 oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, a poloxamer, or a mixture thereof.

97. The pharmaceutical system of claim 90, wherein the hydrophilic surfactant is PEG-20 laurate, PEG-20 oleate, PEG-35 castor oil, PEG-40 palm kernel oil, PEG-40



1 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, polyglyceryl-10  
laurate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, PEG-30  
cholesterol, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether,  
POE-10 oleyl ether, PEG-24 cholesterol, sucrose monostearate, sucrose monolaurate, a  
5 poloxamer, or a mixture thereof.

98. The pharmaceutical system of claim 90, wherein the hydrophilic surfactant  
is PEG-35 castor oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl  
trioleate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides,  
polysorbate 20, polysorbate 80, tocopheryl PEG-1000 succinate, PEG-24 cholesterol, a  
10 poloxamer, or a mixture thereof.

99. The pharmaceutical system of claim 84, wherein the composition  
comprises at least two hydrophilic surfactants.

100. The pharmaceutical system of claim 84, wherein the hydrophobic  
surfactant comprises an un-ionized ionizable surfactant.

15 101. The pharmaceutical system of claim 100, wherein the un-ionized ionizable  
surfactant is the un-ionized form of a surfactant selected from the group consisting of bile  
acids and analogues and derivatives thereof; lecithins, lysolecithin, phospholipids,  
lysophospholipids and derivatives thereof; carnitine fatty acid esters; alkylsulfates; fatty  
acids; acyl lactylates; mono-,diacetylated tartaric acid esters of mono-,diglycerides;  
20 succinylated monoglycerides; citric acid esters of mono-,diglycerides; and mixtures  
thereof.

102. The pharmaceutical system of claim 100, wherein the un-ionized ionizable  
surfactant is the un-ionized form of a surfactant selected from the group consisting of  
lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine,  
25 phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine,  
lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid,  
lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine,  
lactylic esters of fatty acids, stearyl-2-lactylate, stearyl lactylate, succinylated  
monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid  
30 esters of mono/diglycerides, cholic acid, taurocholic acid, glycocholic acid, deoxycholic  
acid, taurodeoxycholic acid, chenodeoxycholic acid, glycodeoxycholic acid,  
glycochenodeoxycholic acid, taurochenodeoxycholic acid, ursodeoxycholic acid,

1 lithocholic acid, tauroursodeoxycholic acid, glyoursodeoxycholic acid, cholylsarcosine,  
N-methyl taurocholic acid, caproic acid, caprylic acid, capric acid, lauric acid, myristic  
acid, palmitic acid, oleic acid, ricinoleic acid, linoleic acid, linolenic acid, stearic acid,  
lauryl sulfate, tetraacetyl sulfate, lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine,  
5 and mixtures thereof.

103. The pharmaceutical system of claim 100, wherein the un-ionized ionizable  
surfactant is the un-ionized form of a surfactant selected from the group consisting of  
lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine,  
phosphatidylglycerol, lysophosphatidylcholine, PEG-phosphatidylethanolamine, lactic  
10 esters of fatty acids, stearyl-2-lactylate, stearyl lactylate, succinylated monoglycerides,  
mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of  
mono/diglycerides, cholic acid, taurocholic acid, glycocholic acid, deoxycholic acid,  
chenodeoxycholic acid, lithocholic acid, ursodeoxycholic acid, taurodeoxycholic acid,  
glycodeoxycholic acid, cholylsarcosine, caproic acid, caprylic acid, capric acid, lauric  
15 acid, oleic acid, lauryl sulfate, lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine,  
and mixtures thereof.

104. The pharmaceutical system of claim 100, wherein the un-ionized ionizable  
surfactant is the un-ionized form of a surfactant selected from the group consisting of  
lecithin, lactic esters of fatty acids, stearyl-2-lactylate, stearyl lactylate, succinylated  
20 monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid  
esters of mono/diglycerides, chenodeoxycholic acid, lithocholic acid, ursodeoxycholic  
acid, taurocholic acid, caprylic acid, capric acid, oleic acid, lauryl sulfate, docusate,  
lauroyl carnitine, palmitoyl carnitine, myristoyl carnitine, and mixtures thereof.

105. The pharmaceutical system of claim 84 wherein the hydrophobic surfactant  
25 comprises at least one compound having an HLB value less than about 10.

106. The pharmaceutical system of claim 105, wherein the hydrophobic  
surfactant is selected from the group consisting of alcohols; polyoxyethylene alkylethers;  
fatty acids; bile acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower  
alcohol fatty acids esters; polyethylene glycol fatty acids esters; polyethylene glycol  
30 glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene  
glycerides; lactic acid derivatives of mono/diglycerides; propylene glycol diglycerides;  
sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-

1 polyoxypropylene block copolymers; transesterified vegetable oils; sterols; sterol  
derivatives; sugar esters; sugar ethers; sucroglycerides; polyoxyethylene vegetable oils;  
polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one  
member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated  
5 vegetable oils, and sterols; and mixtures thereof.

107. The pharmaceutical system of claim 105, wherein the hydrophobic  
surfactant is selected from the group consisting of fatty acids; bile acids; lower alcohol  
fatty acid esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty  
acid esters; polyoxyethylene glycerides; glycerol fatty acid esters; acetylated glycerol fatty  
10 acid esters; lactic acid derivatives of mono/diglycerides; sorbitan fatty acid esters;  
polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block  
copolymers; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable  
oils; reaction mixtures of polyols and at least one member of the group consisting of fatty  
acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures  
15 thereof.

108. The pharmaceutical system of claim 105, wherein the hydrophobic  
surfactant is selected from the group consisting of bile acids; lower alcohol fatty acids  
esters; polypropylene glycol fatty acid esters; propylene glycol fatty acid esters; glycerol  
fatty acid esters; acetylated glycerol fatty acid esters; lactic acid derivatives of  
20 mono/diglycerides; sorbitan fatty acid esters; polyoxyethylene vegetable oils; and mixtures  
thereof.

109. The pharmaceutical system of claim 105, wherein the hydrophobic  
surfactant is a glycerol fatty acid ester, an acetylated glycerol fatty acid ester, or a mixture  
thereof.

25 110. The pharmaceutical system of claim 109, wherein the glycerol fatty acid  
ester is a monoglyceride, diglyceride, or a mixture thereof.

111. The pharmaceutical system of claim 110, wherein the fatty acid of the  
glycerol fatty acid ester is a C<sub>6</sub> to C<sub>22</sub> fatty acid or a mixture thereof.

30 112. The pharmaceutical system of claim 105, wherein the hydrophobic  
surfactant is a reaction mixture of a polyol and at least one member of the group consisting  
of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

1           113. The pharmaceutical system of claim 112, wherein the reaction mixture is a transesterification product of a polyol and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

5           114. The pharmaceutical system of claim 112, wherein the polyol is polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, a saccharide, or a mixture thereof.

10           115. The pharmaceutical system of claim 105, wherein the hydrophobic surfactant is selected from the group consisting of myristic acid; oleic acid; lauric acid; stearic acid; palmitic acid; PEG 1-4 stearate; PEG 2-4 oleate; PEG-4 dilaurate; PEG-4 dioleate; PEG-4 distearate; PEG-6 dioleate; PEG-6 distearate; PEG-8 dioleate; PEG 3-16 castor oil; PEG 5-10 hydrogenated castor oil; PEG 6-20 corn oil; PEG 6-20 almond oil; PEG-6 olive oil; PEG-6 peanut oil; PEG-6 palm kernel oil; PEG-6 hydrogenated palm kernel oil; PEG-4 capric/caprylic triglyceride, mono, di, tri, tetra esters of vegetable oil and sorbitol; pentaerythrityl di, tetra stearate, isostearate, oleate, caprylate, or caprate; 15 polyglyceryl 2-4 oleate, stearate, or isostearate; polyglyceryl 4-10 pentaoleate; polyglyceryl-3 dioleate; polyglyceryl-6 dioleate; polyglyceryl-10 trioleate; polyglyceryl-3 distearate; propylene glycol mono- or diesters of a C<sub>6</sub> to C<sub>22</sub> fatty acid; monoglycerides of a C<sub>6</sub> to C<sub>22</sub> fatty acid; acetylated monoglycerides of C<sub>6</sub> to C<sub>22</sub> fatty acid; diglycerides of C<sub>6</sub> to C<sub>22</sub> fatty acids; lactic acid derivatives of monoglycerides; lactic acid derivatives of 20 diglycerides; cholesterol; phytosterol; PEG 5-20 soya sterol; PEG-6 sorbitan tetra, hexastearate; PEG-6 sorbitan tetraoleate; sorbitan monolaurate; sorbitan monopalmitate; sorbitan mono, trioleate; sorbitan mono, tristearate; sorbitan monoisostearate; sorbitan sesquioleate; sorbitan sesquistearate; PEG 2-5 oleyl ether; POE 2-4 lauryl ether; PEG-2 cetyl ether; PEG-2 stearyl ether; sucrose distearate; sucrose dipalmitate; ethyl oleate; 25 isopropyl myristate; isopropyl palmitate; ethyl linoleate; isopropyl linoleate; poloxamers; cholic acid; ursodeoxycholic acid; glycocholic acid; taurocholic acid; lithocholic acid; deoxycholic acid; chenodeoxycholic acid; and mixtures thereof.

30           116. The pharmaceutical system of claim 105, wherein the hydrophobic surfactant is selected from the group consisting of oleic acid; lauric acid; glyceryl monocaprate; glyceryl monocaprylate; glyceryl monolaurate; glyceryl monooleate; glyceryl dicaprate; glyceryl dicaprylate; glyceryl dilaurate; glyceryl dioleate; acetylated monoglycerides; propylene glycol oleate; propylene glycol laurate; polyglyceryl-3 oleate;

1 polyglyceryl-6 dioleate; PEG-6 corn oil; PEG-20 corn oil; PEG-20 almond oil; sorbitan  
monooleate; sorbitan monolaurate; POE-4 lauryl ether; POE-3 oleyl ether; ethyl oleate;  
poloxamers; cholic acid; ursodeoxycholic acid; glycocholic acid; taurocholic acid;  
lithocholic acid; deoxycholic acid; chenodeoxycholic acid; and mixtures thereof.

5 117. The pharmaceutical system of claim 84, wherein the hydrophobic and  
hydrophilic surfactants are selected from the hydrophobic and hydrophilic members,  
respectively, of the group consisting of sodium lauryl sulfate, oleic acid, linoleic acid,  
monoolein, lecithin, lysolecithin, deoxycholate, taurodeoxycholate,  
glycochenodeoxycholate, polyoxyethylene X-lauryl ether, where X is from 9 to 20,  
10 sodium tauro-24,25-dihydrofusidate, polyoxyethylene ether, polyoxyethylene sorbitan  
esters, p-t-octylphenoxypolyoxyethylene, N-lauryl- $\beta$ -D-maltopyranoside, 1-  
dodecylazacycloheptane-2-azone, and phospholipids, and are each present in an amount of  
greater than 10% by weight, based on the total weight of the pharmaceutical system.

15 118. The pharmaceutical system of claim 84, wherein the hydrophilic  
therapeutic agent is a drug, a vitamin, a nutritional supplement, a cosmeceutical, a  
diagnostic agent, or a mixture thereof.

119. The pharmaceutical system of claim 84, wherein the hydrophilic  
therapeutic agent has an apparent water solubility of at least about 1 mg/mL.

20 120. The pharmaceutical system of claim 84, wherein the hydrophilic  
therapeutic agent is a hydrophilic drug, a cytokine, a peptidomimetic, a peptide, a protein,  
a toxoid, a serum, an antibody, a vaccine, a nucleoside, a nucleotide, a portion of genetic  
material, a nucleic acid, or a mixture thereof.

25 121. The pharmaceutical system of claim 84, wherein the hydrophilic  
therapeutic agent is selected from the hydrophilic members of the group consisting of  
analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, anti-asthma  
agents, anti-bacterial agents, anti-viral agents, anti-coagulants, anti-depressants, anti-  
diabetics, anti-epileptics, anti-fungal agents, anti-gout agents, anti-hypertensive agents,  
anti-malarials, anti-migraine agents, anti-muscarinic agents, anti-neoplastic agents,  
immunosuppressants, anti-protozoal agents, anti-thyroid agents, anti-tussives, anxiolytic,  
30 sedatives, hypnotics, neuroleptics,  $\beta$ -Blockers, cardiac inotropic agents, corticosteroids,  
diuretics, anti-parkinsonian agents, gastro-intestinal agents, histamine H<sub>1</sub>-receptor  
antagonists, keratolytics, lipid regulating agents, muscle relaxants, anti-anginal agents,



1 nutritional agents, analgesics, sex hormones, stimulants, cytokines, peptidomimetics, peptides, proteins, toxoids, sera, antibodies, vaccines, nucleosides, nucleotides, genetic material, nucleic acids, and mixtures thereof.

5 122. The pharmaceutical system of claim 84, wherein the hydrophilic therapeutic agent is selected from the group consisting of acarbose; acyclovir; acetyl cysteine; acetylcholine chloride; alatrofloxacin; alendronate; alglucerase; amantadine hydrochloride; ambenonium; amifostine; amiloride hydrochloride; aminocaproic acid; amphotericin B; antihemophilic factor (human); antihemophilic factor (porcine); antihemophilic factor (recombinant); aprotinin; asparaginase; atenolol; atracurium besylate; atropine; azithromycin; aztreonam; BCG vaccine; bacitracin; becalermine; belladonna; bepridil hydrochloride; bleomycin sulfate; calcitonin human; calcitonin salmon; carboplatin; capecitabine; capreomycin sulfate; cefamandole nafate; cefazolin sodium; cefepime hydrochloride; cefixime; cefonicid sodium; cefoperazone; cefotetan disodium; cefotaxime; cefoxitin sodium; ceftizoxime; ceftriaxone; cefuroxime axetil; cephalixin; 10 cephapirin sodium; cholera vaccine; chronic gonadotropin; cidofovir; cisplatin; cladribine; clidinium bromide; clindamycin and clindamycin derivatives; ciprofloxacin; clondronate; colistimethate sodium; colistin sulfate; corticotropin; cosyntropin; cromalyn sodium; cytarabine; daltaperin sodium; danaproid; deforoxamine; denileukin diftitox; desmopressin; diatrizoate meglumine and diatrizoate sodium; dicyclomine; didanosine; 20 dirithromycin; dopamine hydrochloride; dornase alpha; doxacurium chloride; doxorubicin; editronate disodium; elanaprilat; enkephalin; enoxacin; enoxaprin sodium; ephedrine; epinephrine; epoetin alpha; erythromycin; esmol hydrochloride; factor IX; famciclovir; fludarabine; fluoxetine; foscarnet sodium; ganciclovir; granulocyte colony stimulating factor; granulocyte-macrophage stimulating factor; growth hormones- recombinant human; growth hormone- bovine; gentamycin; glucagon; glycopyrrolate; gonadotropin releasing hormone and synthetic analogs thereof; GnRH; gonadorelin; grepafloxacin; hemophilus B conjugate vaccine; Hepatitis A virus vaccine inactivated; Hepatitis B virus vaccine inactivated; heparin sodium; indinavir sulfate; influenza virus vaccine; interleukin-2; interleukin-3; insulin-human; insulin lispro; insulin procine; insulin NPH; 30 insulin aspart; insulin glargine; insulin detemir; interferon alpha; interferon beta; ipratropium bromide; isofosfamide; japanese encephalitis virus vaccine; lamivudine; leucovorin calcium; leuprolide acetate; levofloxacin; lincomycin and lincomycin



1 derivatives; lobucavir; lomefloxacin; loracarbef; mannitol; measles virus vaccine;  
 meningococcal vaccine; menotropins; mephenzolate bromide; mesalmine; methanamine;  
 methotrexate; methscopolamine; metformin hydrochloride; metoprolol; mezocillin  
 sodium; mivacurium chloride; mumps viral vaccine; nedocromil sodium; neostigmine  
 5 bromide; neostigmine methyl sulfate; neotontin; norfloxacin; octreotide acetate; ofloxacin;  
 olpadronate; oxytocin; pamidronate disodium; pancuronium bromide; paroxetine;  
 pefloxacin; pentamidine isethionate; pentostatin; pentoxifylline; periciclovir;  
 pentagastrin; phentolamine mesylate; phenylalanine; physostigmine salicylate; plague  
 vaccine; piperacillin sodium; platelet derived growth factor-human; pneumococcal vaccine  
 10 polyvalent; poliovirus vaccine inactivated; poliovirus vaccine live (OPV); polymixin B  
 sulfate; pralidoxine chloride; pramlintide; pregabalin; propofenone; propenthaline  
 bromide; pyridostigmine bromide; rabies vaccine; residronate; ribavarin; rimantadine  
 hydrochloride; rotavirus vaccine; salmetrol xinafoate; sincalide; small pox vaccine;  
 solatol; somatostatin; sparfloxacin; spectinomycin; stavudine; streptokinase; streptozocin;  
 15 suxamethonium chloride; tacrine hydrochloride; terbutaline sulfate; thiopeta; ticarcillin;  
 tiludronate; timolol; tissue type plasminogen activator; TNFR:Fc; TNK-tPA;trandolapril;  
 trimetrexate gluconate; trospectinomycin; trovafloxacin; tubocurarine chloride; tumor  
 necrosis factor; typhoid vaccine live; urea; urokinase; vancomycin; valaciclovir; valsartan;  
 varicella virus vaccine live; vasopressin and vasopressin derivatives; vecoronium bromide;  
 20 vinblastin; vincristine; vinorelbine; vitamin B12 ; warfarin sodium; yellow fever vaccine;  
 zalcitabine; zanamavir; zolandronate; and zidovudine.

123. The pharmaceutical system of claim 84, wherein the hydrophilic  
 therapeutic agent is selected from the group consisting of acarbose; acyclovir; atracurium  
 besylate; alendronate; alglucerase; amantadine hydrochloride; amphotericin B;  
 25 antihemophilic factor (human); antihemophilic factor (porcine); antihemophilic factor  
 (recombinant); azithromycin; calcitonin human; calcitonin salmon; capecitabine; cefazolin  
 sodium; cefonicid sodium; cefoperazone; cefoxitin sodium; ceftizoxime; ceftriaxone;  
 cefuroxime axetil; cephalixin; chrionic gonadotropin; cidofovir; cladribine ; clindamycin  
 and clindamycin derivatives; cortocotropin; cosyntropin; cromalyn sodium; cytarabine;  
 30 daltaperin sodium; danaproid; desmopressin; didanosine; dirithromycin; editronate  
 disodium; enoxaprin sodium; epoetin alpha; factor IX; famiciclovir; fludarabine; foscarnet  
 sodium; ganciclovir; granulocyte colony stimulating factor; granulocyte-macrophage

1 stimulating factor; growth hormones- recombinant human; growth hormone- Bovine;  
gentamycin; glucagon; gonadotropin releasing hormone and synthetic analogs thereof;  
GnRH; gonadorelin; hemophilus B conjugate vaccine; Hepatitis A virus vaccine  
inactivated; Hepatitis B virus vaccine inactivated; heparin sodium; indinavir sulfate;  
5 influenza virus vaccine; interleukin-2; interleukin-3; insulin-human; insulin lispro; insulin  
procine; insulin NPH; insulin aspart; insulin glargine; insulin detemir; interferon alpha;  
interferon beta; ipratropium bromide; isofosfamide; lamivudine; leucovorin calcium;  
leuprolide acetate; lincomycin and lincomycin derivatives; metformin hydrochloride;  
nedocromil sodium; neostigmine bromide; neostigmine methyl sulfate; neutontin;  
10 octreotide acetate; olpadronate; pamidronate disodium; pancuronium bromide;  
pentamidine isethionate; pentagastrin; physostigmine salicylate; poliovirus vaccine live  
(OPV); pyridostigmine bromide; residronate; ribavarin; rimantadine hydrochloride;  
rotavirus vaccine; salmetrol xinafoate; somatostatin; spectinomycin; stavudine;  
streptokinase; ticarcillin; tiludronate; tissue type plasminogen activator; TNFR:Fc; TNK-  
15 tPA; trimetrexate gluconate; trospectinomycin; tumor necrosis factor; typhoid vaccine  
live; urokinase; vancomycin; valaciclovir; vasopressin and vasopressin derivatives;  
vinblastin; vincristine; vinorelbine; warfarin sodium; zalcitabine; zanamavir; and  
zidovudine.

20 124. The pharmaceutical system of claim 84, wherein the hydrophilic  
therapeutic agent is selected from the group consisting of acarbose; alendronate;  
amantadine hydrochloride; azithromycin; calcitonin human; calcitonin salmon;  
ceftriaxone; cefuroxime axetil; chrionic gonadotropin; cromalyn sodium; daltaperin  
sodium; danaproid; desmopressin; didanosine; editronate disodium; enoxaprin sodium;  
25 epoetin alpha; factor IX; famciclovir; foscarnet sodium; ganciclovir; granulocyte colony  
stimulating factor; granulocyte-macrophage stimulating factor; growth hormones-  
recombinant human; growth hormone- Bovine; glucagon; gonadotropin releasing hormone  
and synthetic analogs thereof; GnRH; gonadorelin; heparin sodium; indinavir sulfate;  
influenza virus vaccine; interleukin-2; interleukin-3; insulin-human; insulin lispro; insulin  
procine interferon alpha; interferon beta; leuprolide acetate; metformin hydrochloride;  
30 nedocromil sodium; neostigmine bromide; neostigmine methyl sulfate; neutontin;  
octreotide acetate; olpadronate; pamidronate disodium; residronate; rimantadine  
hydrochloride; salmetrol xinafoate; somatostatin; stavudine; ticarcillin; tiludronate; tissue

1 type plasminogen activator; TNFR:Fc; TNK-tPA; tumor necrosis factor; typhoid vaccine  
live; vancomycin; valaciclovir; vasopressin and vasopressin derivatives; zalcitabine;  
zanamavir and zidovudine.

5 125. The pharmaceutical system of claim 84, wherein the composition further  
comprises a solubilizer.

126. The pharmaceutical system of claim 125, wherein the solubilizer is selected  
from the group consisting of alcohols, polyols, amides, esters, propylene glycol ethers and  
mixtures thereof.

10 127. The pharmaceutical system of claim 84, wherein the composition further  
comprises an antioxidant, a bufferant, an antifoaming agent, a detackifier, a preservative, a  
chelating agent, a viscomodulator, a tonicifier, a flavorant, a colorant, an odorant, an  
opacifier, a suspending agent, a binder, a filler, a plasticizer, a lubricant, or a mixture  
thereof.

15 128. The pharmaceutical system of claim 84, wherein the composition further  
comprises an amount of an enzyme inhibiting agent sufficient to at least partially inhibit  
enzymatic degradation of the hydrophilic therapeutic agent.

20 129. The pharmaceutical system of claim 128, wherein the enzyme inhibiting  
agent is P-aminobenzamidine, FK-448, camostat mesylate, sodium glycocholate, an amino  
acid, a modified amino acid, a peptide, a modified peptide, a polypeptide protease  
inhibitor, a complexing agent, a mucoadhesive polymer, a polymer-inhibitor conjugate, or  
a mixture thereof.

25 130. The pharmaceutical system of claim 128, wherein the enzyme inhibiting  
agent is selected from the group consisting of P-aminobenzamidine, FK-448, camostat  
mesylate, sodium glycocholate, aminoboronic acid derivatives, n-acetylcysteine,  
bacitracin, phosphinic acid dipeptide derivatives, pepstatin, antipain, leupeptin,  
chymostatin, elastatin, bestatin, hosphoramindon, puromycin, cytochalasin potatocarboxy  
peptidase inhibitor, amastatin, protinin, Bowman-Birk inhibitor, soybean trypsin inhibitor,  
chicken egg white trypsin inhibitor, chicken ovoinhibitor, human pancreatic trypsin  
inhibitor, EDTA, EGTA, 1,10-phenanthroline, hydroxyquinoline, polyacrylate derivatives,  
30 chitosan, cellulose, chitosan-EDTA, chitosan-EDTA-antipain, polyacrylic acid-  
bacitracin, carboxymethyl cellulose-pepstatin, polyacrylic acid-Bowman-Birk inhibitor,  
and mixtures thereof.

1           131. The pharmaceutical system of claim 84, wherein the composition further comprises an aqueous medium comprising water, an aqueous palatable diluent or an aqueous beverage.

5           132. The pharmaceutical system of claim 131, wherein the therapeutic agent is provided to the system in the aqueous medium.

10           133. The pharmaceutical system of claim 131, wherein the aqueous medium further comprises an amount of an enzyme inhibiting agent sufficient to at least partially inhibit enzymatic degradation of the hydrophilic therapeutic agent, the enzyme inhibiting agent being solubilized, suspended, or partially solubilized and partially suspended, in the aqueous medium.

          134. The pharmaceutical system of claim 84, wherein the composition further comprises a pharmaceutically acceptable acid.

15           135. The pharmaceutical system of claim 134, wherein the acid is selected from the group consisting of hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, carbonic acid, nitric acid, boric acid, phosphoric acid, acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, an amino acid, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, a fatty acid, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, 20 salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and mixtures thereof.

          136. The pharmaceutical system of claim 84, wherein the composition further comprises a pharmaceutically acceptable base.

25           137. The pharmaceutical system of claim 136, wherein the base is an amino acid, an amino acid ester, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrotalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, or a salt of a 30 pharmaceutically acceptable cation and acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, an amino acid, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, a fatty acid, formic acid, fumaric acid, gluconic acid,

1 hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, and uric acid, or a mixture thereof.

5 138. The pharmaceutical system of claim 84, wherein the at least two surfactants are present in amounts such that the composition forms an aqueous dispersion having an average particle size of less than about 200 nm upon mixing with an aqueous diluent.

139. The pharmaceutical system of claim 138, wherein the average particle size is less than about 100 nm.

10 140. The pharmaceutical system of claim 138, wherein the average particle size is less than about 50 nm.

141. The pharmaceutical system of claim 84, wherein the at least two surfactants are present in amounts such that the composition forms an substantially optically clear aqueous dispersion upon mixing with an aqueous diluent.

15 142. The pharmaceutical system of claim 84, wherein the system is substantially free of polyethylene glycol diesters.

143. The pharmaceutical system of claim 84, wherein the system is substantially free of cholesterol.

20 144. The pharmaceutical system of claim 84, wherein the dosage form is substantially free of water.

145. The pharmaceutical system of claim 84 in the form of a preconcentrate in a liquid, semi-solid, or solid form, or as an aqueous or organic diluted preconcentrate.

25 146. The pharmaceutical system of claim 84, wherein the dosage form of the composition is processed by balling, lyophilization, encapsulation, extruding, compression, melting, molding, spraying, spray congealing, coating, comminution, mixing, cryopelletization, spheronization, homogenization, sonication, granulation, or a combination thereof.

147. The pharmaceutical system of claim 84, wherein the dosage form of the composition of is as a pill, capsule, caplet, tablet, granule, pellet, bead or powder.

30 148. The pharmaceutical system of claim 84, wherein the dosage form of the composition is a starch capsule, a cellulosic capsule, a hard gelatin capsule or a soft gelatin capsule.



1           149. The pharmaceutical system of claim 84, wherein the dosage form is formulated for immediate release, controlled release, extended release, delayed release, targeted release, or targeted delayed release.

5           150. The pharmaceutical system of claim 147, which further comprises at least one enteric coating, seal coating, extended release coating, or targeted delayed release coating.

          151. The pharmaceutical system of claim 150, wherein the coating is formed of a material selected from the group consisting of shellac, acrylic polymers, cellulosic derivatives, polyvinyl acetate phthalate, and mixtures thereof.

10           152. The pharmaceutical system of claim 150, wherein the coating is formed of a material selected from the group consisting of Eudragit E, Eudragit L, Eudragit S, Eudragit RL, Eudragit RS, Eudragit NE, Eudragit L.RTM, Eudragit L300.RTM, Eudragit S.RTM, Eudragit L100-55RTM, cellulose acetate phthalate, Aquateric, cellulose acetate trimellitate, ethyl cellulose, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose succinate, polyvinylacetate phthalate, Cotteric, and mixtures thereof.

15           153. The pharmaceutical system of claim 150, wherein the coating is formed of a material selected from the group consisting of Eudragit L.RTM, Eudragit L300.RTM, Eudragit S.RTM, Eudragit L100-55RTM, cellulose acetate phthalate, Aquateric, ethyl cellulose, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose succinate, polyvinylacetate phthalate, Cotteric, and mixtures thereof.

20           154. The pharmaceutical system of claim 84, wherein the dosage form of the composition is a solution, suspension, emulsion, cream, ointment, lotion, suppository, spray, aerosol, paste, gel, drops, douche, ovule, wafer, troche, cachet, syrup or elixir.

25           155. The pharmaceutical system of claim 84, wherein the dosage form is a multiparticulate carrier coated onto a substrate with the composition.

          156. The pharmaceutical system of claim 155, wherein the substrate is a particle, a granule, a pellet or a bead, and is formed of the therapeutic agent, a pharmaceutically acceptable material, or a mixture thereof.

30           157. The pharmaceutical system of claim 155, wherein the multiparticulate carrier is coated with at least one enteric coating, seal coating, extended release coating, or targeted delayed release coating.



1           158. The pharmaceutical system of claim 155, wherein the dosage form is further processed by encapsulation, compression, extrusion, molding, spheronization or cryopelletization.

5           159. The pharmaceutical system of claim 155, wherein the dosage form is further processed to form a starch capsule, a cellulosic capsule, a hard gelatin capsule, or a soft gelatin capsule.

          160. The pharmaceutical system of claim 159, wherein the capsule is coated with at least one enteric coating, seal coating, extended release coating, or targeted delayed release coating.

10          161. The pharmaceutical system of claim 84, wherein the hydrophilic therapeutic agent is present in the dosage form of the composition.

          162. The pharmaceutical system of claim 161, wherein the hydrophilic therapeutic agent is solubilized in the composition, suspended in the composition, or partially solubilized and partially suspended in the composition.

15          163. The pharmaceutical system of claim 84, wherein the hydrophilic therapeutic agent is present in a dosage form separate from the dosage form of the composition.

          164. The pharmaceutical system of claim 84, wherein the dosage form of the composition is formulated for oral, mucosal, pulmonary, nasal, vaginal, transmembrane, buccal or rectal administration.

          165. The pharmaceutical system of claim 163, wherein the dosage form of the hydrophilic therapeutic agent is formulated for oral, mucosal, pulmonary, nasal, vaginal, transmembrane, buccal or rectal administration.

25          166. An absorption enhancing composition for co-administration to a patient with a hydrophilic therapeutic agent, the composition comprising an effective amount of an absorption enhancer comprising at least two surfactants, at least one of which is hydrophilic, the absorption enhancing composition being substantially triglyceride free.

30          167. The composition of claim 166, wherein the effective amount is an amount sufficient to increase the rate, the extent, or both the rate and extent, of bioabsorption of a hydrophilic therapeutic agent, when the composition and the hydrophilic therapeutic agent are administered to a patient.

1           168. The composition of claim 166, wherein the effective amount is an amount  
sufficient to improve the consistency of the rate, the extent, or both the rate and extent, of  
bioabsorption of a hydrophilic therapeutic agent. when the composition and the  
hydrophilic therapeutic agent are administered to a patient.

5           169. The composition of claim 166, which further comprises a hydrophilic  
therapeutic agent.

170. A method of controlling the rate, the extent, or both the rate and extent, of  
bioabsorption of a hydrophilic therapeutic agent administered to a patient, the method  
comprising:

10           (a) providing a dosage form of an absorption enhancing composition,  
the composition comprising at least two surfactants, at least one of which is  
hydrophilic, and being substantially free of triglycerides;

          (b) providing a hydrophilic therapeutic agent; and

          (c) administering the dosage form of the absorption enhancing  
15 composition and the hydrophilic therapeutic agent to the patient.

171. The method of claim 170, wherein the hydrophilic therapeutic agent is  
provided in the dosage form of the absorption enhancing composition.

172. The method of claim 171, wherein the hydrophilic therapeutic agent is  
solubilized, suspended, or partially solubilized and partially suspended, in the dosage form  
20 of the absorption enhancing composition.

173. The method of claim 170, wherein the hydrophilic therapeutic agent is  
provided in a dosage form separate from the dosage form of the absorption enhancing  
composition.

174. The method of claim 173, wherein the step of administering comprises  
25 administering the dosage form of the absorption enhancing composition and co-  
administering the dosage form of the hydrophilic therapeutic agent.

175. The method of claim 170, wherein the dosage form of the absorption  
enhancing composition is formulated for oral, mucosal, pulmonary, nasal, vaginal,  
transmembrane, buccal or rectal administration.

30           176. The method of claim 173, wherein the dosage form of the hydrophilic  
therapeutic agent is formulated for oral, mucosal, pulmonary, nasal, vaginal,  
transmembrane, buccal or rectal administration.

- 1           177.   The method of claim 170, wherein the patient is a mammal.  
          178.   The method of claim 170, wherein the patient is a human.

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/18807

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/00, 9/14, 9/16, 9/20, 9/22, 9/28, 9/48

US CL : 424/451, 456, 457, 464, 489

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/451, 456, 457, 464, 489

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
Please See Extra Sheet.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,858,398 A (CHO) 12 January 1999, abstract, columns 11-18, examples and claims.	1-178



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

28 SEPTEMBER 2000

Date of mailing of the international search report

20 NOV 2000

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/18807

## B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

WEST

search terms: hydrophilic, hydrophobic, surfactants, phospholipids, sterols, cholesterol, pills, tablets, capsules, powders, beads.